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PROPHYLAXIS AGAINST LETHAL EFFECT OF HIGH ALTITUDE BY MEANS OF A DIGITALIS GLYCOSIDE (GITALIN)

ERNST FISCHER, M.D.
RICHMOND, VA.

IN THE course of a comprehensive investigation concerning the relation between drug susceptibility and high altitude, the remarkable prophylactic action of gitalin against the lethal effect of the severe anoxia produced by high altitude became evident. Since this protective action of digitalis might be of some importance in aviation medicine, the experimental data on this prophylactic effect are presented now, without waiting for the complete results of the originally planned investigation.

METHODS

Male mice (from the same colony) which weighed 16 to 30 Gm. were used. For each experiment thirty mice of approximately equal weight (± 3 Gm.) were divided into two groups of fifteen, each of equal weight distribution. A 0.1 per cent gitalin solution was prepared by dissolving the gitalin in as little 95 per cent alcohol as possible, and then diluting the alcoholic solution with Tyrode solution to the desired volume. Of the final solution, amounts containing 2.5 to 10.0 gamma* per Gm. were injected intraperitoneally into the members of one of these groups. In preliminary experiments the L. D_{-50}† was established at about 30 gamma per Gm. Both groups, the protected and the control, were kept under identical conditions (for four to seventy-two hours), and later exposed simultaneously to low pressure in a big glass desiccator used as a decompression chamber, simulating altitudes between 30,000 and 34,000 feet. Accumulation of carbon dioxide was avoided by using a pump capable of maintaining the desired pressure despite an adequate air flow. Decompression was produced gradually and as uniformly as possible. A pressure corresponding to 22,000 feet was reached in three minutes, and the final altitude in the next three minutes. Return to normal pressure occurred in a corresponding way. The duration of the exposures as given in the tables includes not only the time the final pressure was maintained, but also half of the time during which the pressure changed from that of 22,000 feet to the final altitude, or vice versa. Despite all of the care that was taken to perform the experiments as

From the Department of Physiology and Pharmacology, Medical College of Virginia, Richmond, Va.

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*1 gamma = $\frac{1}{1000}$ mg.

†The dose per gram which is fatal to 50 per cent of the animals given that amount.

uniformly as possible, the susceptibility of the mice to high altitude varied very much from one experiment to another. Apparently, the age of the mice, their average weight, and the humidity and temperature of the atmosphere are factors influencing the high altitude susceptibility. However, in simultaneous experiments with two uniform groups of mice or with a normal group and a group of mice which had received in advance 0.01 c.c. per Gm. of Tyrode solution intraperitoneally, the difference in mortality was small (±4.2 per cent). Therefore, the difference in mortality which was observed between the gitalin group and the control group of each experiment was more or less a measure of the protection afforded. If twelve died in the control group, and only six in the protected group, the actual protection was 50 per cent. However, a simple consideration demonstrates that this actual protection percentage does not mean much, since it depends to a certain extent on the duration of the exposure. If, in the same experiment, the exposure had been much shorter, the result could have been one death in the control series and no death in the protected group, which would be an actual protection of 100 per cent. With increased duration of exposure, the result could have been fifteen fatalities in the control series and any number between six and fifteen fatalities in the protected group. However, with a reasonable degree of

TABLE I

GITALIN PROPHYLAXIS AGAINST LETHAL EFFECT ON HIGH ALTITUDE. DEPENDENCE OF PROBABLE PROTECTION FACTOR ON ALTITUDE

EXP. NO.	DOSE GAMMA PER GRAM	INTERVAL BETWEEN PROPHYLAXIS AND EXPOSURE		EXPOSURE		DEATH RATIO		PROBABLE PROTECTION FACTOR*
		HOURS	MIN.	FEET	TIME MIN.	CONTROL	PROTECT.	
D 20	5.0	23	18	30,000	17	11/15	3/15	56.3
D 21	10.0	23	36	30,000	62	4/15	1/15	47.5
D 24	5.0	24	12	30,000	30	11/15	6/15	43.9
mean	5-10	23	42	30,000	36	26/45	10/45	48.5
D 1	2.5	26	20	30,000	25	6/15	2/15	23.3
D 2	5.0	4	22	32,000	15	9/15	3/15	53.3
D 7	5.0	8	0	32,000	23	3/15	0/15	60.0
D 5	3.75	21	0	32,000	13	11/15	5/15	47.2
D 22	5.0	24	3	32,000	20	14/15	5/15	61.8
D 23	5.0	24	12	32,000	8	12/15	3/15	67.5
D 17	5.0	25	6	32,000	7	14/15	4/15	69.1
mean	5.0	24	25	32,000	12	40/45	12/45	65.1
D 4	3.75	24	40	33,000	11	11/15	2/15	70.8
D 8	5.0	21	43	33,000	7	10/15	1/15	75.8
mean	3.75-5	23	21	33,000	9	21/30	3/30	72.6
D 13	10.0	5	0	34,000	9	14/15	7/15	48.3
D 9	5.0	6	6	34,000	5	12/15	8/15	30.0
D 3	3.75	6	32	34,000	8	8/15	4/15	38.3
D 10	5.0	16	20	34,000	6	12/15	0/15	90.0
D 6	5.0	20	36	34,000	7	11/15	0/15	86.6
D 14	10.0	24	44	34,000	7	15/15	3/15	80.0
D 15	5.0	24	52	34,000	6	14/15	1/15	89.7
D 16	10.0	25	0	34,000	4	15/15	0/15	100.0
D 18	10.0	25	43	34,000	6	14/15	3/15	75.9
D 12	5.0	29	6	34,000	4	15/15	1/15	93.3
mean	5-10	23	46	34,000	6	96/105	8/105	87.7
D 11	5.0	45	23	34,000	4	14/15	6/15	55.2
D 26	5.0	50	17	34,000	8	14/15	4/15	68.1
D 19	5.0	69	51	34,000	6	15/15	13/15	13.3
D 25	5.0	72	23	34,000	10	9/15	5/15	35.5

*For explanation and calculation of "probable protection factors," see text.

probability one can assume that with prolongation of the exposure up to the moment when the last mouse of the control group was dying, at most no more additional mice of the protected group will have succumbed than in the control. This would mean, in the example mentioned, a total mortality of 15/15 in the control and of 9/15 in the protected group, resulting in a minimum protection of 40 per cent. The mean between the actual protection and the minimum protection can be regarded as the probable protection, called in this paper "probable protection factor," after omitting the percentage sign.

RESULTS

Table I summarizes the experiments arranged according to altitude and time interval between prophylactic injection of gitalin and decompression. The probable protection procured depends on the final altitude and on the magnitude of the dose of gitalin. Optimal protection for each altitude is secured by doses of 5 to 10 gamma per Gm. for a period from sixteen until thirty hours after prophylaxis (compare figures in Table I). If one calculates the average probable protection factor for all experiments in which the animals were exposed to the same altitude and treated at the proper time with a sufficient dose, it becomes obvious that the protection factor increases linearly with the altitude (Fig. 1 *A*). The protection at 34,000 feet is 180.8 per cent of that at 30,000 feet. On account of this strict relation between altitude and protection factor, it is possible, despite the limited number of experiments, to find out the relation between magnitude of dose and protec-

TABLE 11

GITALIN PROPHYLAXIS AGAINST LETHAL EFFECT OF HIGH ALTITUDE. INFLUENCE OF MAGNITUDE OF DOSE UPON PROBABLE PROTECTION FACTOR

(INJECTIONS 16 TO 30 HOURS BEFORE EXPOSURE)

EXP. NO.	DOSE GAMMA PER GRAM	EXPOSURE		DEATH RATIO		PROBABLE PROTECTION FACTOR*	PROBABLE PROTECT. FACTOR CORRECTED FOR 34,000 FT.*
		FEET	TIME MIN.	CONTROL	PROTECT.		
D 1	2.5	30,000	25	6/15	2/15	23.3	42.1
D 5	3.75	32,000	13	11/15	5/15	47.2	60.7
D 4	3.75	33,000	11	11/15	2/15	70.8	79.8
mean	3.75	32,500		22/30	7/30	59.1	71.2
D 20	5.0	30,000	17	11/15	3/15	56.3	100.0
D 24	5.0	30,000	30	11/15	6/15	43.9	79.5
D 22	5.0	32,000	20	14/15	5/15	61.8	79.6
D 23	5.0	32,000	8	12/15	3/15	67.5	87.0
D 8	5.0	33,000	7	10/15	1/15	75.0	85.5
D 6	5.0	34,000	7	11/15	0/15	86.6	86.6
D 10	5.0	34,000	6	12/15	0/15	90.0	90.0
D 12	5.0	34,000	4	15/15	1/15	93.3	93.3
D 15	5.0	34,000	6	14/15	1/15	89.7	89.7
mean	5.0	32,550		108/135	23/135	73.1	87.9
D 21	10.0	30,000	62	4/15	1/15	47.5	85.9
D 14	10.0	34,000	7	15/15	3/15	80.0	80.0
D 16	10.0	34,000	4	15/15	0/15	100.0	100.0
D 18	10.0	34,000	6	14/15	3/15	75.9	75.9
mean	10.0	33,000		48/60	7/60	76.7	85.3

*For explanation and calculation of "probable protection factors" and their correction for other altitudes, see text and legend for Fig. 1.

tion. All experiments in which the prophylactic injections were given sixteen to thirty hours in advance are summarized and arranged according to the magnitude of the dose in Table II, and their probable protection factors, if necessary, corrected for an altitude of 34,000 feet. Maximal protection is reached, probably in an S-shaped curve, at 5 grains, and doubling this dose does not alter the protection significantly (Fig. 1 *B*). No attempt was made to use doses above 10 grains, because in preliminary experiments for the determination of the L. $D._{50}$ a dose of 15 gamma occasionally had lethal effects. The time course of the prophylactic effect of a single but optimal gitalin injection (5 to 10 gamma per Gm.) is demonstrated by Fig. 1 *C*, in which the protection factors (corrected for 34,000 feet, if necessary) are plotted against the time elapsed between injection and altitude exposure.

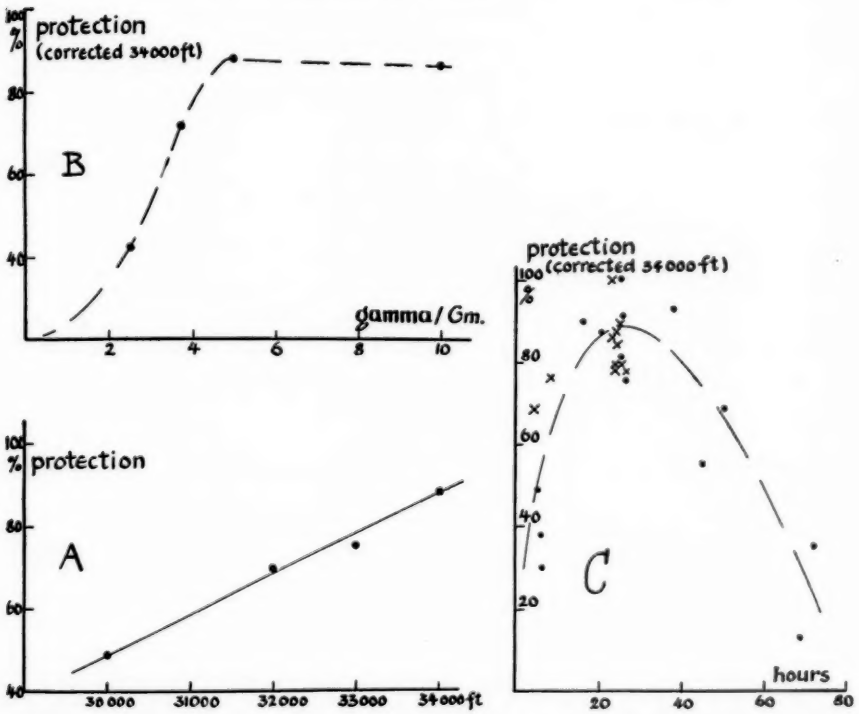

Fig. 1.—*A*, Average probable protection produced by intraperitoneal injection into mice of 5 to 10 gamma per Gm. of gitalin sixteen to thirty hours previous to exposure to low barometric pressure corresponding to various altitudes. *B*, Average probable protection produced by giving various doses of gitalin sixteen to thirty hours in advance. Before calculating the average protection, the protection factor for experiments not conducted at 34,000 feet was corrected for that altitude according to the linear relation in *A*. *C*, Time course of the probable protection afforded by 5 to 10 gamma per Gm. of gitalin. Black dots represent experiments conducted at 34,000 feet. *X*, experiments at lower altitude, but protection factor corrected for 34,000 feet.

DISCUSSION

The experiments reported here demonstrate clearly the prophylactic value of gitalin against exposure to a high altitude, but do not indicate

in any way by what mechanism this protection is brought about. In normal subjects during severe exercise, Groscurth and Bansi,[1] as well as Parade,[2] observed an increase in efficiency after nontoxic doses of digitalis. The latter investigator explains these results by the experimentally proved fact that digitalis diminishes the alkali reserve loss which occurs normally during physical exercise. A similar mechanism could be assumed for the high altitude prophylaxis. However, experiments in which it was attempted to influence by various means (e.g., NH_4Cl, $NaHCO_3$) the normal shift in alkali reserve during exposure to high altitude have thus far failed to demonstrate any protective effects. On the contrary, the susceptibility to high altitude was distinctly increased by interference in any direction with the alkali reserve. Another possible mechanism of the gitalin prophylaxis described here might be diminution of the anoxemic dilatation of the heart, as reported by Van Liere and co-workers.[3] Probably the gitalin effect results in an improvement of cardiovascular function. Armstrong[4] found in his own experimental work on rats that, at high altitudes (25,000 feet), death was usually caused by depression of the respiratory center, not by circulatory failure. In my experiments on mice, however, there were some indications that, especially at higher altitudes, the circulation stops at a time when the respiratory center is still active. My observations, made by mere inspection, revealed that in those experiments in which death occurred after a few minutes, acute circulatory failure was the main cause of death, whereas in those experiments in which death occurred only after a longer exposure, respiratory failure was responsible for death. This difference in the mechanism of death is probably responsible for the increased gitalin protection at higher altitude, for with increased altitude death occurs more quickly.

Macht,[5] as well as Lehman and Hanzlik,[6] have reported that high altitude (about 10,000 feet) distinctly increases the susceptibility of cats and pigeons to digitalis. Since their experiments dealt only with the emetic and fatal doses of digitalis, they do not have much in common with the experiments reported here. The fact that increasing the dose from 5 to 10 gamma does not improve the prophylactic effect might indicate some harmful influence of the larger dose, although the latter is only one-third of L. $D._{50}$ at sea level.

SUMMARY

Gitalin, when given to mice in doses of 5 to 10 gamma per Gm. intraperitoneally, has a high prophylactic effect against the severe, acute anoxemia produced by low atmospheric pressures corresponding to altitudes of 30,000 to 34,000 feet. The protection is at its height for a period of sixteen to thirty hours after injection. The protection afforded increases with the altitude, and reaches nearly 90 per cent at 34,000 feet.

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LOW VOLTAGE OF THE QRS WAVES IN THE ELECTROCARDIOGRAM, WITH ESPECIAL REFERENCE TO LEAD IV

C. Edward Leach, M.D., Wellford C. Reed, M.D., and Paul D. White, M.D.
Boston, Mass.

THE present study was begun in an attempt to establish the significance of low voltage of the QRS complex in the precordial lead of the electrocardiogram in the presence of normal voltage in the standard leads. Three groups of 100 cases each were analyzed for comparison. Group 1 comprised cases with low voltage in the three classical leads but not in Lead IV (Fig. 1). Group 2 showed normal QRS voltage in the classical leads and low voltage in the fourth lead alone (Fig. 2). Group 3 had low voltage of QRS in all four leads (Figs. 3 and 4). Low voltage was considered to be present in the limb leads if the QRS complexes showed maximal deflections in either direction from the base line of not more than 5 mm. in any of the three leads. In the precordial lead a maximal deflection of 5 mm. or less of the QRS complex in either direction was likewise considered to be low voltage. These measurements were made from the top of the base line to the peak of the R wave, or from the bottom of the base line to the lowest point of the S wave if the downward deflection was the greater in amplitude. In collecting the cases no attempt was made toward selection, and none was eliminated

Table I

General Data of Whole Series

Low voltage QRS (300 cases)	Average age	Sex		Body build			Heart disease		Congestive failure		ECG other than voltage	
		M	F	Thin	Obese	Average	+	0	+	0	Normal	Abnormal
Group 1 (100) Leads I, II, III	55	68	32	29	27	44	65	35	31	69	25	75
Group 2 (100) Lead IV only	51	21	79	14	47	39	47	53	9	91	42	58
Group 3 (100) Leads I, II, III, IV	55	33	67	24	35	41	63	37	26	74	20	80

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from the series because of associated electrocardiographic abnormalities, except that inaccurately standardized tracings were not used. In general, the patients were representative of the cases studied routinely in the cardiac laboratory of the Massachusetts General Hospital during the course of three years (1936-1939), having been referred from both private services and public wards as well as from the outpatient department.

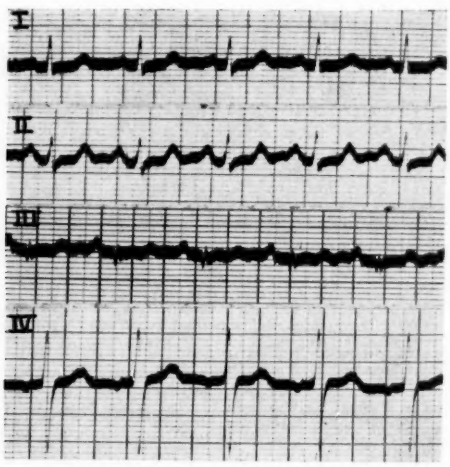


Fig. 1.—Electrocardiograms of male, aged 65 years, of average build. Coronary heart disease with mild angina pectoris. Low QRS voltage in the classical leads but not in Lead IV.

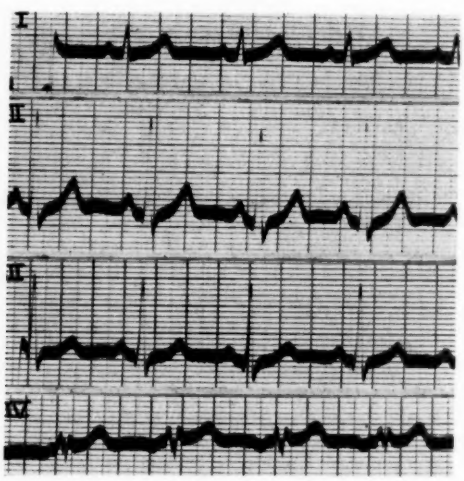


Fig. 2.—Electrocardiograms of thin female, aged 47 years. No heart disease; menopause syndrome. Normal QRS voltage in the classical leads and low in Lead IV.

Striking differences were found in the results derived from the three groups (Table I). The sex ratio was essentially reversed in Groups 2 and 3 as compared with Group 1. Women greatly outnumbered men

in the groups with low voltage of QRS in Lead IV, and men predominated to about the same degree in the group with normal QRS voltage in Lead IV. There were also greater numbers of obese patients in Groups 2 and 3, especially in Group 2, than in Group 1. Heart disease, heart failure, and electrocardiographic abnormalities (including

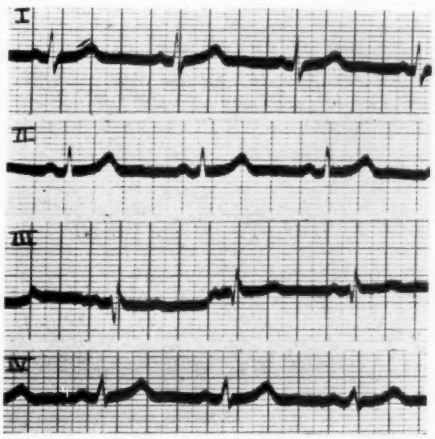


Fig. 3.—Electrocardiograms of obese female, aged 47 years. No apparent heart disease. Poor posture. Low QRS voltage in all four leads.

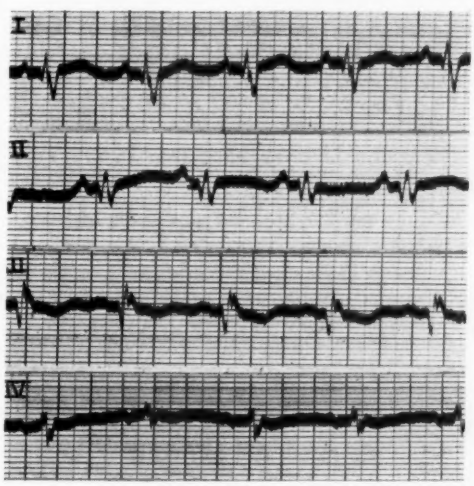


Fig. 4.—Electrocardiograms of moderately obese female, aged 66 years. Coronary heart disease with old myocardial infarction, mild cardiac failure, and pulmonary infarcts. Low QRS voltage in all four leads and bundle branch block.

changes other than T-wave inversion in Lead III and premature beats) predominated to approximately the same degree in Groups 1 and 3. In Group 2, however, the majority of subjects did not have heart disease or associated electrocardiographic abnormalities, and the incidence of heart failure in these persons was practically nil. The quality of the heart sounds roughly paralleled the incidence of heart failure, as did in-

crease in heart size, but these differences between the various groups were not striking and the blood pressure level seemed to be of little or no significance.

TABLE II

ETIOLOGY IN MODERATE AND SEVERE CARDIAC CONDITIONS

LOW QRS	CORONARY-HYPERTENSIVE	CORONARY ALONE	CORONARY OCCLUSION, WHOLE GROUP	HYPERTENSIVE ALONE	RHEUMATIC	MISCELLANEOUS*
Group 1 (57), Leads I, II, III alone	12 (21%)	31 (54%)	25 (44%)	0	6 (11%)	8 (14%)
Group 2 (36), Lead IV alone	18 (50%)	6 (17%)	3 (8%)	5 (14%)	4 (11%)	3 (8%)
Group 3 (58), Leads I, II, III, IV	15 (26%)	29 (50%)	21 (36%)	1 (2%)	10 (17%)	3 (5%)

*Includes syphilitic, cor pulmonale, pericarditis, congenital, thyroid, calcareous aortic stenosis.

We then analyzed the cases from the standpoint of the etiology of the heart disease (Table II). Here again the patients with low voltage in the standard leads alone showed findings roughly parallel with those of the patients who had low voltage in all four leads. When the QRS complexes were low in the chest lead only, hypertension was more often a factor, either with or without coronary disease. The differences of the percentages of this factor were striking, but they can probably be explained by the higher ratio of women and of obesity in Group 2 and by the milder heart disease.

In addition to the variation in the results among the three groups, one other fact immediately attracted our attention, namely, that the entire series showed a lower incidence of heart disease than we had anticipated. A previous report from this laboratory[1] had indicated that low voltage of QRS in the standard leads of the electrocardiogram was, as a rule, a serious prognostic sign except when accompanying temporary toxic states. Of the fifty-seven patients studied at that time, thirty-four had coronary disease, and all of the rest had other types of heart disease, myxedema, or other serious generalized disease. Hepburn and Jamieson[2] and Turner[3] reported similar findings. Although Willius and Killins[4] did not agree, they had eliminated electrocardiograms abnormal for other reasons from their series and thus had eliminated many of the more serious cardiac cases, so that their results were not strictly comparable with ours. The variation of results in our present series from those of previous reports led us to a further search of the literature for an explanation, and we have found many reports since 1922 which, taken together with our present study, tend to clarify the subject.

Cohn and Raisbeck[5, 6] showed that varying the relationship of the leads to the heart changed the electrical axis recorded. Meek and Wilson,[7] using open-chested dogs and varying the position of the heart, likewise produced changes in the recorded

electrical axis. Contrary to current opinion, they found that rotation around an anteroposterior axis was not important, but that rotation around the heart's longitudinal axis gave the picture of preponderance of one or the other ventricle. Otto[8] applied the same reasoning and the same procedure to the problem of low voltage and found that tipping the apex of the heart upward on a transverse axis through the base produced low recorded voltage of both QRS and T waves in the limb leads. Katz and Ackerman[9] confirmed the work of Otto and of Meek and Wilson and showed that the voltage of both ectopic and normal sinus beats was lowered by these procedures. The effect of the position of the body in producing changes in electrical axis and voltage has been demonstrated by Sigler[10] and Stewart and Bailey,[11] especially good illustrations being shown in the latter paper.

Eyster and co-workers,[12] by cutting or removing various tissues adjacent to the heart, showed that the conduction of currents away from the heart was by means of preferential pathways and that the electrical field of the heart approximated a plane. This was confirmed by Katz and Korey,[13] who produced a lowering of the recorded potential in the limb leads by insulating various proximal structures from the heart with rubber sheeting. The large posterior muscle group, the chest wall itself, and the diaphragm were found to be good conductors, while the lungs and great vessels were poor ones. They felt that these findings nullified the principles of the Einthoven triangle, since the recorded axis seems to depend on the parts of the heart in contact with the good conductors rather than the heart's relationship to any particular electrical vector.

Wilson,[14] in discussing the principles of the Einthoven triangle, pointed out on theoretical grounds that an increase in the conductivity of tissues in contact with the heart should also lower the recorded voltage in the limb leads. He considered as the possible responsible factors for low voltage in any given case: (1) lowered potential produced by a diseased condition of the heart muscle; (2) accidental neutralization of effects of different parts of the heart; and (3) changes in conductivity of tissues adjacent to the heart. Katz and his co-workers[15] confirmed this by the introduction of good conductors between the heart and the usual conducting pathways, producing low voltage of the records, presumably by the introduction of shunts or by bringing into contact with the pathways larger areas of the heart muscle and thereby producing neutralizing effects. As suggested by Wilson, pleural effusions, pericardial effusions, adhesions, and pulmonary consolidation or edema would act in a similar manner, probably accounting for some of the discrepancies observed in the axis shifts in cases of pneumothorax and pleural effusion.[16, 17] To obviate the possibility that the open thorax plays a role, Katz and his group repeated their study of the conducting pathways, closing the thorax each time.[18] Their findings were essentially the same this time, except that they used a different method in severing the great vessels and concluded that they actually accounted for a considerable proportion of the conduction of currents.

We found no reported series with standard technique for the application of Lead IV in which the voltage had been specifically studied. However, several authors[19-23] have pointed out that the position of the chest electrode is important with reference to the relative sizes of R and S waves and, to a lesser extent, to the maximum potential recorded. Hoffman and Delong[19] stated that the voltage was usually greater when the anterior electrode was close to the apex of the heart and also that the voltage of the chest lead was not necessarily parallel to that of the limb leads. Katz and Kissin[24] felt that low voltage was due to: (1) intraventricular block, (2) a relative shunt of currents away from the electrodes, or (3) a change in the position of the heart, making the long axis more perpendicular to the plane of the leads. They suggested that discrepancies between the voltage in limb leads and in the chest lead might differentiate "shunts" from changes in the position of the heart. Goldbloom[25] found low voltage in the chest lead only in cases of coronary

disease, but his normal series (twenty-five cases) was small, and Master[20] in 104 normal adults noted low voltage of the chest lead sometimes when the anterior electrode was placed outside of the cardiac apex. Roth's illustrations[21] were interesting because they showed variations in the voltage of the QRS complexes on shifting the indifferent as well as the chest electrode. The effects of shifting the position of the chest electrode were studied specifically by Edwards and VanderVeer,[26] who confirmed the impressions of the others that the main changes were in the relative sizes of the R and S waves, but their tracings also showed variations in the maximum potential.

Using these data from the literature we separated our cases into cardiac and noncardiac groups and attempted to evaluate them on the basis of the presence or absence of probable explanations for the occurrence of low voltage (Table III). In the category of extracardiac disease, we included conditions which we felt should affect the body as a whole, such as severe infections, anemia, malnutrition, hypothyroidism, uremia, etc., and those which would change the conductivity of tissues in the chest, such as pulmonary fibrosis, consolidation, effusions, pulmonary edema, etc. We then considered as other probable factors conditions which would alter the position of the heart, such as abnormal body builds, emphysema, spinal deformities, abdominal disease elevating the diaphragm, etc. In the cases of low voltage in Lead IV we considered the female sex and obesity as probable factors because of the likelihood of errors in placement of the chest electrode. It seemed wise to compare the results in the noncardiac subjects with those in moderate and severe cardiac patients only, leaving out cardiac patients who were asymptomatic and without enlargement, since it was unlikely that such a mild degree of heart disease in itself could play a role in the production of low voltage.

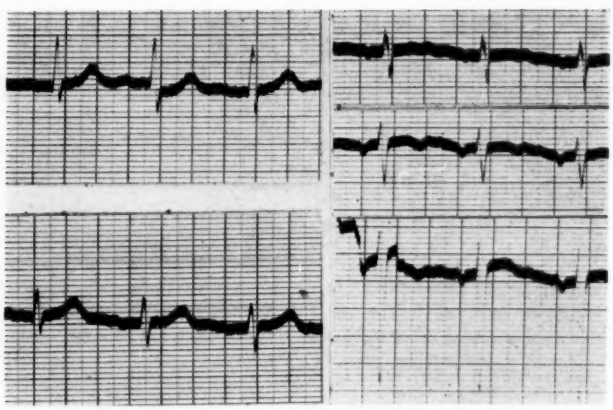
The results of this analysis, shown in Table III, were instructive in several points. In all three groups there was more extracardiac disease in the cardiac cases than in the noncardiac cases, mainly because of the inclusion of the signs of heart failure, but this finding was considerably less frequent in Group 2 than in the others. Factors such as abnormal body build, etc., were about equally divided in all three groups between the cardiac and noncardiac subjects, but Group 2 contained a much greater percentage of these cases. Of the twenty-four cardiac patients who had no failure, other disease, or other apparent factors, seventeen had had coronary thrombosis, three had bundle branch block, and two each had marked left axis deviation and pericarditis —in other words, evidence of considerable heart disease. We were then left with thirty persons who were apparently entirely healthy physically and who had no evident explanation of any sort for the presence of low voltage in the electrocardiograms, an incidence of 10 per cent of the whole series. Of these, eighteen (6 per cent) showed low voltage in the classical leads and seven (2 per cent) in all four leads. These percentages are considerably higher than those reported by Shipley and Halloran[27] and Chamberlain and Hay[28] in normal subjects.

TABLE III

COMPARISON OF FACTORS OTHER THAN HEART DISEASE

LOW VOLTAGE QRS (300 CASES)	EXTRACARDIAC DISEASE IN			OTHER PROBABLE FACTORS IN			NO APPARENT EXTRACARDIAC FACTORS IN		
	MODERATE AND SEVERE CARDIAC PATIENTS	NON-CARDIAC PATIENTS	MILD CARDIAC PATIENTS	MODERATE AND SEVERE CARDIAC PATIENTS	NON-CARDIAC PATIENTS	MILD CARDIAC PATIENTS	MODERATE AND SEVERE CARDIAC PATIENTS	NON-CARDIAC PATIENTS	MILD CARDIAC PATIENTS
Group 1 (100), Leads I, II, III only	36 (63%)	13 (37%)	3 (38%)	7 (12%)	4 (11%)	1 (13%)	14 (24%)	18 (51%)	4 (50%)
Group 2 (100), Lead IV only	15 (42%)	17 (32%)	2 (18%)	18 (50%)	31 (58%)	8 (73%)	3 (8%)	5 (9%)	1 (9%)
Group 3 (100), Leads I, II, III, IV	41 (71%)	21 (57%)	3 (60%)	10 (17%)	9 (24%)	1 (20%)	7 (12%)	7 (19%)	1 (20%)

McFarland and his associates,[29] however, have studied 173 normal healthy aviators and found low voltage of the QRS complexes in the classical leads alone in 8 per cent, in Lead IV alone in 5 per cent, and in all four leads in one case (0.6 per cent). Furthermore, 30 per cent of their entire series showed voltage in the classical leads of less than 0.8 mv. All of these electrocardiograms were normal in other respects, and there was no obvious explanation for the occurrence of low voltage in any of these cases.

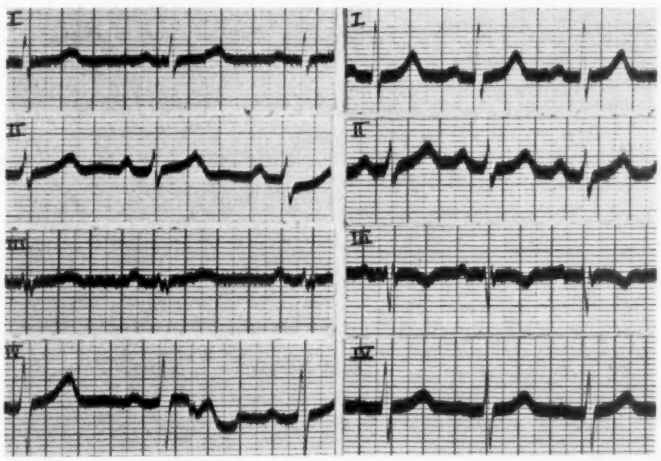


A. *B.*

Fig. 5.—Chest leads in different patients. *A*, Both tracings were taken at the apex of the heart in an obese woman, showing the effect of breast tissue on the voltage of the chest lead. The upper record was taken with the precordial electrode placed at the cardiac apex and *underneath* the thick, pendulous breast; the lower record, with the electrode at the cardiac apex but *overlying* the breast. *B*, Electrocardiograms of woman of average build, with firm breast. Low voltage in both strips at the apex, with the electrode, first, so far as possible underneath the breast and, second, overlying the breast, but normal voltage in the lowest strip at the left sternal border.

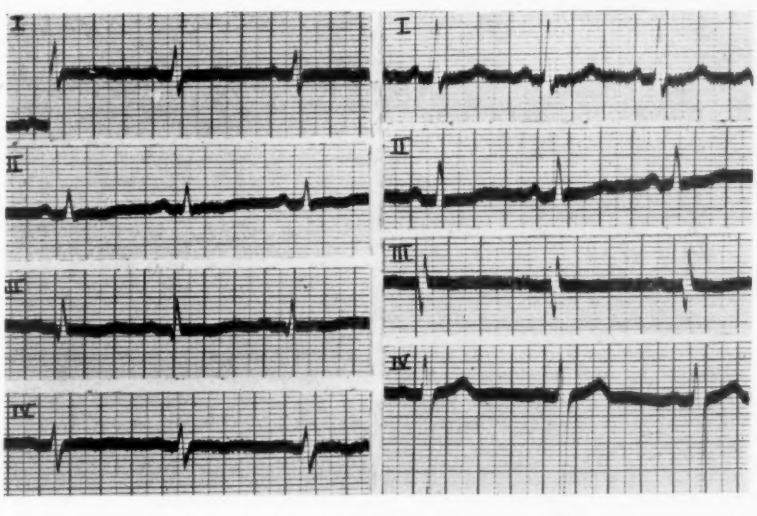
During the analysis of our series we were impressed by the fact that the voltage was extremely variable in many of the cases without any comparable changes in the condition of the patients. This was especially true in Lead IV, and it seemed likely that variation in placing the chest electrode was a factor of significance. Twenty patients were studied with this in mind, and it was found, as other authors had already noted, that the voltage changed as the electrode was moved to various other positions on the chest. Furthermore, the voltage fluctuated with different phases of respiration in some patients, and in others, placing the electrode under the breast at the apex of the heart resulted in a normal recorded voltage when the voltage had been low with the electrode over the breast at the apex. Apparently the amount of tissue between the heart and the electrode was as important as the position of the electrode with reference to the frontal plane of the heart (Fig. 5). In male patients it followed that a thick chest wall or obesity might account for low voltage in Lead IV in a similar manner as in females, and although we had no way of adequately testing this theory, it was observed in a few cases that loss of a pathologic amount of excess weight was followed

by a return of the voltage to normal in the chest lead, and in at least one patient loss of weight resulted in a return to normal of low voltage in the classical leads (Fig. 6).



A. *B.*

Fig. 6.—Electrocardiograms of obese female, aged 17 years. No apparent heart disease, but possibly rheumatic fever. *A*, At 160 pounds; *B*, at 143 pounds.



A. *B.*

Fig. 7.—Four lead electrocardiograms before (*A*) and after (*B*) treatment of myxedema with thyroid extract. The patient was a slightly obese female, aged 58 years, with no evident heart disease.

In clear-cut myxedema, the QRS voltage tends to be distinctly low in all four leads and is amplified to the usual normal range by thyroid therapy (Fig. 7).

After obtaining the data from our complete series of 300 cases, we wondered whether different figures might be obtained from cases of

extremely low voltage, for instance, 0.3 mv. or less. Ten such cases were found in Group 1, twenty-six in Group 2, and five in Group 3, and they were tabulated separately according to the criteria for the entire series. Heart disease of some degree was more frequently found in these cases than in those with voltage up to 0.5 mv., but only in those from Group 3 was significant (moderate or severe) heart disease more common, and the small number of cases (five) in this group made the comparison inconclusive. The incidences of extracardiac disease and of other probable causative factors were slightly higher than in the entire series, the importance of female sex in relation to low voltage in Lead IV being especially well shown. In the cases of very low voltage in Lead IV only, the incidence of moderate and severe heart disease was only about one-half of that in the entire Group 2 and extracardiac factors were relatively much more important. Conversely, not a single case with a voltage of 0.3 mv. or less lacked an adequate explanation of some kind for the occurrence of low voltage.

Apparently, the factors producing low voltage of the QRS complexes were more obvious with more extreme lowering of the voltage, but heart disease did not appear to be any more important in the extreme cases than in the more moderate ones, and other causative factors seemed to be present in about the same ratio regardless of the degree of reduction in the voltage. In fact, it was our impression during the original selection of cases that a voltage of 0.7 mv. was just as significant as 0.5 mv. and occurred for the same reasons, although of milder degree. Such cases were omitted from this study, however, and we therefore have no statistical data to support this belief.

DISCUSSION

As a result of this study and review of the literature, it appears that low voltage of the QRS complex of the electrocardiogram occurs for many different reasons, and in any single case it is difficult to say which factor is responsible. Body build, the position of the heart or of the chest electrode, and increase in conductivity of adjacent tissues are all apparently of considerable importance. The heart lesion per se seems less important than the manifestations of congestive failure that sometimes result. In the absence of heart failure, the most common finding in the cardiac group is myocardial infarction. However, in our entire series, significant heart disease was found in only about one-half of the persons with low voltage in the standard leads or in all four leads, and in only about one-third of those with low voltage in the chest lead alone. Heart size, the quality of heart sounds, and the blood pressure level bore no very definite relationship to the occurrence of low voltage. In general, the finding of low voltage per se, in the classical leads or in the chest lead, has not much diagnostic value regarding the presence or absence of heart disease. The serious import which has at times been ascribed to low voltage of the QRS waves is doubtless dependent on ac-

companying electrocardiographic abnormalities, especially in the shape and direction of the QRS waves and the shape and direction of the T waves. It is true, however, that more than one-half of all our patients with low QRS voltage, less commonly in Group 2, had such other electrocardiographic abnormalities, and the presence of low voltage paralleled the appearance of congestive failure. To that extent, the low QRS voltage is significant in relation to heart disease. The important point from this analysis is that low QRS voltage alone is not indicative of heart disease or, necessarily, of any other trouble, as Willius pointed out years ago, but is apparently dependent on variations in the relationship of the position of the heart to the leads themselves or to the manner in which the currents are conducted away from the heart.

SUMMARY

Analysis was made of 300 cases showing low voltage of the QRS complexes of the electrocardiogram. Three groups of 100 cases each were compared with one another; Group 1 having low voltage of QRS in the classical leads but normal voltage in the precordial (fourth) lead, Group 2 having low voltage of QRS in the fourth lead alone, and Group 3 having low QRS complexes in all four leads.

Evidence of heart disease was found in only 57 per cent of the entire series, and only 47 per cent of the group with low voltage in the chest lead alone had evidence of heart disease.

Generalized debilitating diseases, changes in the position of the heart, and changes in the conductivity of adjacent tissues seemed to be important factors in the production of low voltage of the QRS complexes. Furthermore, the thickness of the chest wall and the position of the precordial electrode influenced the voltage of QRS in Lead IV.

Heart disease was of no greater relative importance than extracardiac factors in cases showing extreme reduction in QRS voltage (for instance, 0.3 mv. or less). However, in such cases the responsible factor was likely to be more obvious than in cases with moderate degrees of low voltage.

Analysis of the literature likewise indicates the importance of the factors mentioned above.

Even in the patients with considerable heart disease, fluctuations in the voltage, with changes in the state of compensation, suggested that the heart lesions were of less importance than the secondary manifestations of heart failure in the production of lowered potential.

Ten per cent of the entire series showed no evident explanation of any sort for the occurrence of low voltage, being apparently healthy normal persons in every respect.

Our study indicates that the solitary finding of low voltage of the QRS complexes is of little or no diagnostic value regarding the presence or absence of heart disease or of any other trouble. The wider use of

electrocardiograms on normal people outside of hospitals will probably show a higher incidence of low voltage than the literature suggests at present.

We are indebted to Dr. Sherman Golden for help in the collection of cases at the beginning of this study.

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CONTINUOUS VASODILATATION IN THE EXTREMITIES PRODUCED REFLEXLY: PHYSIOLOGIC STUDIES ON TEMPERATURE OF SKIN AND ON VOLUME FLOW OF BLOOD

GEORGE E. BROWN, JR., M.D.* AND EDGAR V. ALLEN, M.D.,†
ROCHESTER, MINN.

THE purpose of this study was to develop a method of increasing the blood flow to extremities to maximal or nearly maximal levels and of maintaining it in this state. Such a method has long been considered ideal for the treatment of patients with occlusive arterial diseases when the usual volume flow of blood is less than that which can be obtained by treatment.

There are many types of treatment for chronic occlusive arterial diseases and each has been followed by clinical evidence of improvement according to various observers.[1] One or more objections, however, are applicable to almost all methods. From some types of treatment, the oral administration of large amounts of sodium chloride,[2, 3] for example, there is no evidence of increased blood flow. From several other procedures there is lack of agreement among various investigators that circulation improves. From others improvement is only temporary, as it is after the intravenous injection of typhoid vaccine: the improved circulation appears to persist only a few hours longer than the fever, although repeated injections may improve the circulation permanently. The equipment necessary for some methods of treatment is expensive or cumbersome. This is true of the intermittent suction and pressure apparatus and the Sanders oscillating bed.

We have desired a method of treatment to which such objections cannot be offered. It should unquestionably increase the volume flow of blood to the extremities. It should be inexpensive and simple of application in order that it could be used in the patients' homes. It should be so constructed that it could be applied more or less continuously, and naturally it should not harm the patient. The data which we will present later in this paper indicate that we have made progress in the development of such a method of treatment.

Direct application of heat to limbs in which it is desired to increase the circulation causes an increased flow of blood but has two disadvantages: ischemic limbs are easily burned and the local warmth increases the tissue metabolism in the heated limb. This increase in metabolism utilizes some of the oxygen and other nutrients which are

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*Fellow in Medicine, The Mayo Foundation.

†Division of Medicine, The Mayo Clinic.

brought by the increased flow of blood and thus some of the benefits are neutralized.[4]

The principle of reflex vasodilatation, that is, the induction of vasodilatation by applying heat to an extremity other than the one being studied, has been known since Sewell and Sanford[5] observed in 1890 that immersion of one hand in hot water (48° C.) increased the volume flow of blood in the opposite extremity. Winkler[6] in 1902 observed flushing of rabbits' ears when the hindquarters were immersed in hot water. Stewart,[7] in 1911, decided that immersion of one arm in hot water increased blood flow in the opposite extremity, for the loss of heat, measured calorimetrically, was increased from the extremity opposite to the immersed one. In 1931, Lewis and Pickering[8] found that the temperature of the skin of the digits of human subjects could be increased by warming the body which was enclosed in a heating cabinet from which the extremities protruded. Gibbon and Landis[9] and Landis and Gibbon[10] showed that an increase in temperature of the skin of the toes could be produced by immersing the forearms in warm water. Similar observations were made by Grant and Holling,[11] Freeman,[4] and Wright and Phelps.[12] Pickering,[13] Pickering and Hess,[14] and Landis and Gibbon[10] have shown that reflex vasodilatation depends on venous blood returning from the warmed extremity (afferent limb of the reflex arc) and on the sympathetic nervous system (efferent limb of the reflex arc). These observations have been confirmed by Fatherree and Allen.[15]

THE HEATING UNIT

To apply the principle of reflex vasodilatation we suggested a heating unit which was constructed for us by the Colvinex Corporation through the kindness of Mr. Paul Gaynes, the president. The apparatus consists of a fine copper wire woven by a special process onto a fireproof cloth. This is incorporated into a waterproof and washable cover. A transformer reduces the voltage to 10; a fuse protects against short circuits, and a thermostat included in the units prevents the temperature from increasing to more than 43° C. Although these units probably can be improved further in some details, the principle of their use seems established. We have tentatively designated the units as "heating sleeve" and "heating boot" as applied to the upper and lower extremities, respectively.

PLAN OF STUDY

Twelve normal individuals and thirteen patients with hypertension were studied under controlled conditions. Tobacco and food were withheld for twelve hours preceding the study. The subjects were placed at rest in the supine position in a room in which the temperature was maintained about 22° C. Changes of position and psychic disturbances were eliminated as much as possible to avoid extraneous influences.[16-18]

The temperature of the skin of the fingers and toes was measured by the Sheard electromotive thermometer.[19] The circulation was considered to be in a basal state when the temperature of the skin remained at a fairly constant level. Usually an hour was required for this stabilization.

Fig. 1.—The heating sleeve applied to the arm. A heating boot can be applied to the leg in a similar manner.

The blood flow in an arm of each of nine of the twelve normal individuals and of ten of the thirteen patients with hypertension was measured with the plethysmograph. The blood flow was determined for the basal state. Then the preheated heating sleeve was applied to the upper extremity which was not in the plethysmograph (Fig. 1).* The temperature of the skin of the other three extremities including the one in the plethysmograph was recorded every ten minutes. Determinations of blood flow were made with the plethysmograph at various stages of vasodilatation. When the temperature of the skin reached a maximal level, the blood flow then determined was designated "the blood flow of maximal skin temperature."

The term "vasodilatation" is used throughout this paper because of common usage, although "arteriolar dilatation" would be better because it designates the mechanism by which the volume flow of blood is increased.

RESULTS

Skin Temperatures.—The temperature of the skin of the toes of all but two of the normal subjects and of all but one of the patients with hypertension increased in response to the application of the heating

*Some of our patients have used the units continuously for several days without harm. A mild erythema, which disappeared promptly, has been noted, however.

sleeve to a forearm and hand. All individuals studied had an increase in the temperature of the skin of the fingers of the opposite hand. The response in one case is shown in Fig. 2. A high level of vasodilatation which we believe is indicated by the high level of skin temperature was produced and maintained as long as the heating sleeve was applied. On removal of the unit, the fingers and toes quickly cooled.

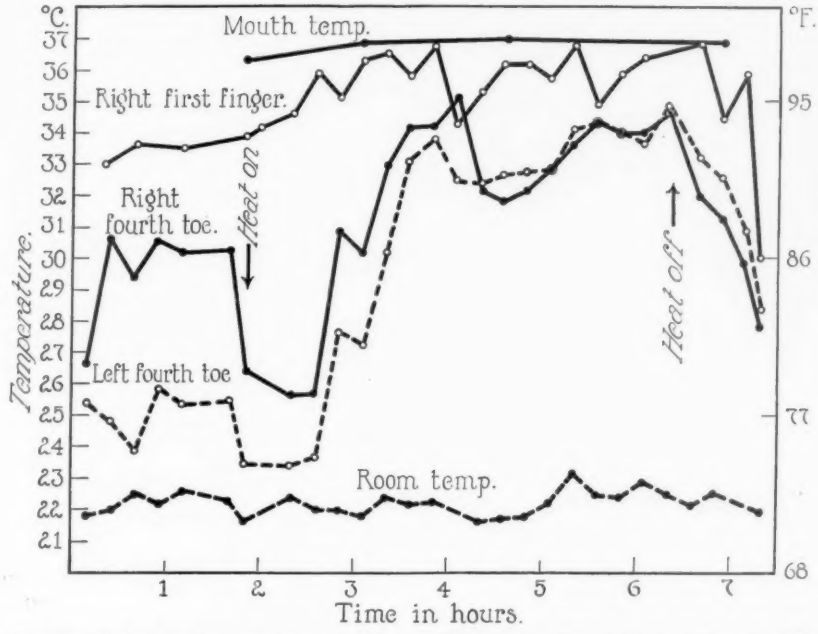

Fig. 2.—Effect on temperature of skin of toes and of the right first finger of the application of the heating sleeve to the left arm. The temperature of the skin of the right first finger increased 2.1° C. and that of the right and left fourth toes, 9.4° and 11.5° C. respectively (Table I, Case 1).

Failures of vasodilatation such as occurred in three of our cases have been noted when other methods have been used.[8, 9] Failure seems related to inadequate heat which is applied to inadequate body surface. The three cases in which vasodilatation did not occur in the toes were excluded from further consideration in the study on temperatures of the skin.

For the normal individuals the mean basal temperature of the right fourth toe was 27° C. and the mean basal temperature of the left fourth toe was 26.5° C. The mean maximal temperatures of the respective toes were 33.9° C. and 33.6° C. The mean basal temperature of the fourth finger on the left hand was 30.6° C. and the mean of the highest reading was 35.5° C. (Table I). The mean increase in the temperature of the skin of the respective toes was 6.9° C. and 7.0° C. and the mean increase in the temperature of the skin of the fingers was 4.9° C.

In the group of patients with hypertension, the mean basal temperature of the right fourth toe was 28.4° C. and of the left fourth toe 28.3°

C. The mean maximal temperatures were 34.6° and 33.8° C., respectively. The mean basal and maximal temperatures of the skin of the fourth finger on the left hand were 32.6° and 35.9° C., respectively (Table II).

TABLE I

EFFECT OF APPLYING A HEATING SLEEVE TO THE RIGHT UPPER EXTREMITY ON THE TEMPERATURE OF THE SKIN OF THE DIGITIS OF NORMAL SUBJECTS

CASE	TEMPERATURE OF SKIN IN DEGREES C					
	FOURTH TOES				FOURTH LEFT FINGER	
	RIGHT		LEFT			
	BASAL	MAXIMAL	BASAL	MAXIMAL	BASAL	MAXIMAL
1*	25.6	35.0	23.2	34.7	34.5†	36.6†
2	21.5	35.4	20.7	34.9	25.6	36.2
3	23.6	32.9	23.0	33.0	28.6	35.8
4	25.3	34.5	28.7	35.2	31.6	36.0
5	27.9	34.0	28.6	33.8	33.0	35.3
6	30.6	33.9	30.6	33.6	33.5	35.6
7	32.8	35.0	32.9	34.6	28.8	34.8
8	29.5	34.4	25.1	30.2	31.0	35.2
9	21.6	31.0	21.3	32.4	27.1	36.8
10‡	31.4	32.7	31.2	33.5	32.0	32.5
Range	21.5-32.8	31.0-35.4	20.7-32.9	30.2-35.2	25.6-34.5	32.5-36.8
Mean	27.0	33.9	26.5	33.6	30.6	35.5

*Heating sleeve was on left upper extremity.
†Temperatures from right first finger.
‡In cases 11 and 12 the temperature of the skin of the toes did not increase.

TABLE II

EFFECT OF APPLYING A HEATING SLEEVE TO THE RIGHT UPPER EXTREMITY ON THE TEMPERATURE OF THE SKIN OF THE DIGITS OF PATIENTS WITH HYPERTENSION

CASE	TEMPERATURE OF SKIN IN DEGREES C					
	FOURTH TOES				FOURTH LEFT FINGER	
	RIGHT		LEFT			
	BASAL	MAXIMAL	BASAL	MAXIMAL	BASAL	MAXIMAL
13	25.3	34.6	25.8	34.2	35.6	36.8
14	33.4	34.0	33.2	34.9	36.1	36.2
15	24.0	31.0	24.5	32.4	32.0	36.0
16	27.0	33.5	26.0	33.5	29.0	35.8
17	22.0	33.0	22.0	33.1	30.0	36.3
18	28.6	36.5	28.0	36.0	31.0	36.8
19	24.1	36.4	24.0	26.3	31.0	35.8
20	31.9	34.8	32.8	32.8	34.0	34.7
21	33.0	34.9	33.1	35.2	34.1	35.8
22	26.5	35.0	25.5	34.4	31.9	35.4
23	33.5	35.8	33.6	36.0	32.0	35.6
24*	31.3	35.9	30.6	36.4	34.5	36.0
Range	22.0-33.5	31.0-36.5	22.0-33.6	26.3-36.4	29.0-36.1	34.7-36.8
Mean	28.4	34.6	28.3	33.8	32.6	35.9

*In Case 25 the temperature of the skin of the toes did not increase.

The mean increase in the temperature of the skin of the respective toes was 6.2° and 5.5° C., and in the temperature of the skin of the fingers, 3.3° C.

Blood Flow.—The blood flow of all of the nineteen subjects studied increased in the arm opposite the one heated. The response of one individual is shown in Fig. 3. The blood flow increased from a basal

TABLE III

THE EFFECT OF APPLYING A HEATING SLEEVE TO THE OPPOSITE ARM ON THE VOLUME FLOW OF BLOOD TO AN UPPER EXTREMITY OF NORMAL SUBJECTS. DETERMINATIONS MADE WITH A PLETHYSMOGRAPH

CASE	BLOOD FLOW PER MINUTE PER 100 C.C. OF ARM TISSUE				PERCENTAGE INCREASE IN BLOOD FLOW
	BASAL STATE	STATUS OF VASODILATATION (DETERMINED BY SKIN TEMPERATURE)			
		MILD	MODERATE	MAXIMAL	
1	2.10	2.68	3.47	4.68	123
2	2.43	4.18	6.04	7.63	214
3	2.55	4.30	6.93	5.10	100
4	4.94	7.36	12.36	16.08	226
5	1.64	2.22	2.70	2.88	76
6	2.98	4.56	4.33	8.45	184
7	2.42	4.38	5.19	7.39	205
8	1.64	1.60	2.72	2.88	76
11	2.63	4.10	6.03	7.46	184
Range	1.64-4.94	1.60-7.36	2.70-12.36	2.88-16.08	76-226
Mean	2.59	3.93	5.53	6.95	168

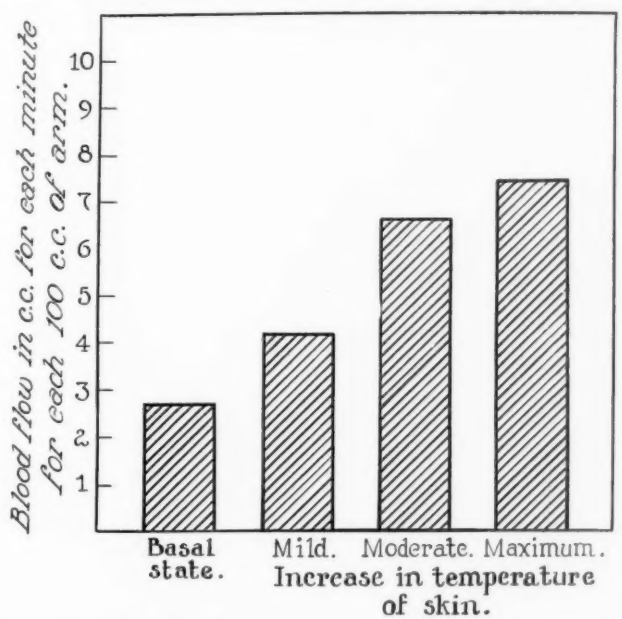

Fig. 3.—The increased volume flow of blood in one arm resulting from application of a heating sleeve to the other arm (Table III, Case 11).

level of 2.63 c.c. per minute per 100 c.c. of arm to 7.56 c.c. per minute per 100 c.c. of arm. This was an increase of 184 per cent. The average blood flow for the nine normal individuals (Table III) was 2.59 c.c. per

minute per 100 c.c. of arm in the basal state. The average blood flow determined when the temperature of the skin was maximal was 6.95 c.c. per minute per 100 c.c. of arm, or an average increase of 168 per cent.

TABLE IV

THE EFFECT OF APPLYING A HEATING SLEEVE TO THE OPPOSITE ARM ON THE VOLUME FLOW OF BLOOD TO THE UPPER EXTREMITY OF PATIENTS WITH HYPERTENSION. DETERMINATIONS MADE WITH THE PLETHYSMOGRAPH

CASE	BLOOD FLOW PER MINUTE PER 100 C.C. OF ARM TISSUE				PERCENTAGE INCREASE IN BLOOD FLOW
	BASAL STATE	STATUS OF VASODILATATION (DETERMINED BY SKIN TEMPERATURE)			
		MILD	MODERATE	MAXIMAL	
15	5.64	6.04	9.16	9.97	77
16	1.65	1.91	3.71	5.16	213
17	1.47	1.90	2.00	1.74	18
18	3.24	3.79	4.53	5.50	70
20	1.92			2.25	17
21	3.80			5.65	49
22	4.05			7.59	87
23	2.93			7.49	156
24	2.53			14.50	473
25	2.55	3.07	4.06	7.72	203
Range	1.47-5.64	1.90-6.04	2.00-9.16	1.74-14.50	17-473
Mean	2.98	3.34	4.69	6.76	127

In the series of cases of hypertension similar increases in the blood flow were noted (Table IV). The average blood flow determined in these cases at basal state was 2.98 c.c. per minute per 100 c.c. of arm. The average blood flow determined at maximal skin temperature was 6.76 c.c. per minute per 100 c.c. of arm. There was an average increase in blood flow of 127 per cent in the arm in response to the application of a heating sleeve to the opposite arm.

For four individuals the blood flows of the forearm and hand and then of the forearm alone were determined. The latter calculation was made by occluding the arterial circulation at the wrist. These studies indicate that the percentage increase in circulation to the hand was usually greater than in that to the forearm.

There may have been some inaccuracies in the measurement and calculation of the blood flow with the plethysmograph. Thus figures for blood flow are approximate and not absolute values. Any inaccuracies which may have been present appear to be constant, and the relation of the various figures given for the calculation of blood flow in the same extremity of the same subject is probably accurate. Studies which are incomplete at present indicate that increases in temperature of the skin occur in the presence of chronic occlusive arteriolar diseases when the heating sleeve is used, although the increases are not so great as those of normal individuals. Also, studies indicate that the effects on circulation just reported persist as long as the heating unit is applied.

PROPOSED CLINICAL USE

At present we can only theorize about the clinical value of these units. Their use, however, might contribute substantially to reduction of the incidence of venous thrombosis, thrombophlebitis and pulmonary embolism following operation. Smith, Craig, and one of us (Allen)[20, 21] have shown that after operation the venous blood flow ordinarily slows up. This factor is probably important in the genesis of the postoperative complications just mentioned. Moreover these observers have shown that when the skin is warm, blood flows rapidly in the veins, and when the skin is cold, blood flows slowly in the veins.[20, 21] Hence use of the heating boot or sleeve after operations should prevent the slowing of the venous circulation which ordinarily occurs and perhaps prevent or diminish the postoperative complications mentioned.

The units might well replace hot, moist packs in some instances such as in the treatment of phlebitis. A unit might be modified for the purpose of keeping moist dressings hot. This would find ready application in the treatmert of cellulitis, lymphangitis, phlebitis, and similar conditions. In the treatment of arthritis and painful joints attributable to other causes, these units should be useful for they allow the application of heat continuously for long periods. Dr. C. H. Slocumb, of the Clinic, believes that these units afford the most satisfactory method of applying heat locally to arthritic joints. The physical therapist may find other uses.

The heating sleeve and heating boot should be valuable in increasing the blood flow in limbs in which it is diminished because of chronic arterial occlusion. The blood supply can be increased through collateral arteries which are not occluded. In disorders such as arterial embolism, in which vasospasm plays a major role, an increase in blood supply should be attained by release of this vasospasm.

Theoretically these heating units have advantages which many other methods used to improve the circulation do not have; further clinical experience is necessary before their therapeutic value can be evaluated accurately. Investigations of this nature are in progress and will be reported later.

SUMMARY AND CONCLUSIONS

The following conclusions can be drawn from our data concerning the response to application of the heating sleeve to an upper extremity.

1. The temperature of the skin of the digits of all the other extremities increases in most instances.

2. The volume flow of blood of the opposite upper extremity increases and probably a similar effect is produced in the lower extremities because the temperature of the skin of the toes usually increases.

Studies on the clinical value of these units are in progress. Several conditions in which they might be used advantageously have been suggested.

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DISCUSSION

DR. NORMAN E. FREEMAN, Philadelphia.—The observations which we have made, both at Boston and Philadelphia, are entirely in agreement with those that Dr. Allen and Dr. Brown have described. Dr. Landis and Dr. Gibbon, in 1934, described the vasodilatation test in which heat was applied to two of the extremities and the skin temperature was measured in the other two. The procedure which Dr. Allen and Dr. Brown have shown us is essentially the one which we are using today routinely in the Vascular Clinic in order to measure the capacity for vasodilatation.

In the Vascular Clinic of the University of Pennsylvania in the past five years over a thousand vasodilatation tests have been performed on patients with various degrees of arterial occlusion. At first, Dr. Landis thought that this procedure might be therapeutically effective as a means of increasing blood flow after arterial occlusion, just as Dr. Allen has suggested. He did not take up this type of treatment because he found in a large series of cases that the more the arterial obstruction the less vasodilatation was possible.

In observations on the blood flow through the hand, when heat was applied to the body, we found that, when the circulation was badly occluded, as in advanced Buerger's disease, it was impossible to get an increase in the blood flow. When the tissues are in jeopardy so that the local demand for blood cannot be satisfied, I think that there is already a maximum stimulus for arterial inflow, and that reflex vasodilatation will not increase the circulation.

Therefore, when the need is greatest, in pregangrene cases, there is least success with this type of treatment. In the vasospastic group of cases it is very helpful, because a condition of prolonged increase in blood flow can be maintained without harm to the patient and with relatively little expense and trouble. I think that this is a field in which Dr. Allen's therapeutic suggestion will be worth while.

DR. D. I. ABRAMSON, Cincinnati.—I should like to ask Dr. Allen whether he would consider this treatment of use in cases in which there is a decrease in blood supply to the muscle. It would seem that, from most of the evidence presented thus far, the so-called Landis response takes place in the skin vessels and not in the muscle vessels.

DR. EDGAR V. ALLEN, Rochester, Minn.—Dr. Freeman's point is a very good one. This method of treatment will not make blood flow through arteries which are occluded organically. However, it is almost invariably true that, when there is chronic occlusion of the main arteries, there is also further impairment of the circulation as a result of either vasospasm or incomplete vasodilatation. One may almost always improve the circulation by various means in extremities in which blood flow is diminished chiefly because of organic changes. I do not know that our method is any better or any worse than other methods of improving the circulation, but theoretically, at least, it is just as good if it produces increases in the temperature of the skin and in blood flow as other methods of treatment do.

I do not think it has been reliably demonstrated that sympathectomy and fever, for example, increase the blood flow only to the skin and not to the muscle. The studies so far have been based largely upon measurement of the temperature of the muscle, and it has not been shown that this is a reliable method of estimating blood flow in muscle. Be that as it may, in chronic occlusive arterial disease gangrene does not affect the muscle of the calf, for example, but affects the skin of the digits. Hence I think it is of little moment whether or not this method increases the flow of blood to the muscle in the calf of the leg. If one can improve the circulation to the skin of the digits of a patient with chronic occlusive arterial disease, then he has done something which is of value from the standpoint of treatment. It is almost certain that improvement in the circulation to the muscle of distal parts of the extremities is increased likewise.

THE AURICULOVENTRICULAR RATIO AND ITS RELATIONSHIP TO THE ELECTRICAL AXIS OF THE HEART

A. Henry Clagett, Jr., M.D.
Providence, R. I.

THE aim of this study was to determine the relationship, if any, between the roentgenologic auriculoventricular (A-V) ratio and the electrical axis of the heart, and, in doing so, to determine the reliability of the A-V index as related to clinical medicine.

In 1898, Rummo,[1] an Italian clinician and anatomist, described, without the aid of the x-ray, a line on the cardiac silhouette corresponding to the auriculoventricular septum. However, he made no mention of an auriculoventricular index.

The A-V ratio was first described in 1911 by Van Zwaluwenburg and Warren,[2] who drew, in addition to the long diameter of the cardiac silhouette (Fig. 1, *DG'*), a line from the junction of the right auricle and the diaphragm to the junction of the pulmonary conus and the left ventricle (*D'G*). They admitted that this line did not represent exactly the auriculoventricular septum either in position or direction, but proceeded to assume that the two cardiac areas so produced roughly represented the auricular and ventricular areas. They then reasoned that if there were two similar segments, with a common base and the obliquity of the axis was equal, the areas would be in proportion to the fractional diameters *DX* and *XG'*, and that the ratio *DX:XG'* would roughly represent the surface relations of the auricles and ventricles.

Applying this new ratio to a small series of normal persons (number of cases not mentioned), they found that the normal values lay between 0.534 and 0.704. They then applied this ratio to a series of sixty abnormal hearts and found that all patients with mitral stenosis gave a value exceeding 0.880, even when complicated with mitral regurgitation. Patients with uncomplicated mitral regurgitation had values between 0.657 and 0.834. One patient with aortic insufficiency had a value of 0.378. The patients with arteriosclerosis had values between 0.282 and 0.393, due, the authors claimed, to the lengthening of the arch of the aorta, with a resulting low and transverse position of the heart. The value for one patient with arteriosclerosis was 0.492. This was considered to be a discrepancy and was explained on the basis of an irregular pulse.

From the Heart Station of the Rhode Island Hospital, Providence; Frank T. Fulton, M.D., Director.

Abridgement of thesis submitted to the Faculty of the Graduate School of Medicine of the University of Pennsylvania, in partial fulfillment of the requirements for the degree of Master of Medical Science (M.Sc. [Med.]) for graduate work in Cardiology

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In 1920, Van Zwaluwenburg[3] again mentioned the A-V ratio, claiming the normal to be about 0.55. He stated that the largest ratio he had encountered was 1.42 (in a case of mitral stenosis) and that the smallest was 0.25 (in a well-compensated case of aortic regurgitation). At this time he presented an objection to the ratio, stating that the auriculo-diaphragmatic junction was not fixed and depended largely upon the height of the diaphragm.

In the same year Vaquez and Bordet[4] mentioned the work of Van Zwaluwenburg and Warren, but made no further observations or criticism of the A-V ratio.

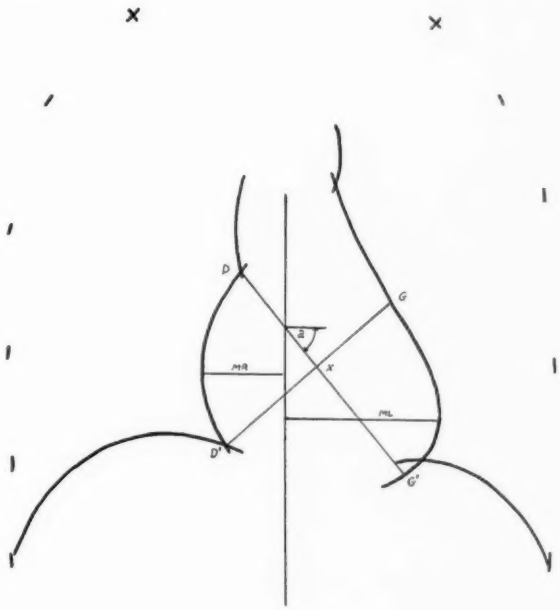

Figure 1.

The ratio was not mentioned again until 1932 when Levene and Reid[5] included it in an article concerning differential diagnosis of cardiac enlargement by use of the x-ray. They restated the normals attained by the previous writers, but arbitrarily chose values exceeding 0.800 as being indicative of auricular enlargement and values less than 0.500 as being caused by enlarged ventricles. An interesting table for differential diagnosis by means of roentgen ray measurement (modified from Vaquez[6]) was presented.

The same authors[7] in the same year stated that, contrary to popular belief, mitral stenosis occurs before mitral regurgitation in rheumatic heart disease affecting the mitral valve. They claimed that the old conception was due to the difficulty in recognizing early stenosis, and

they suggested as a means of diagnosis of early stenosis the use of the A-V ratio. They illustrated their theory with a series of patients supposed to have mitral stenosis, all having an increased A-V ratio. This material was entirely clinical, no pathologic evidence being presented.

With the material in these studies showing that conditions associated with left ventricular preponderance (arteriosclerotic heart disease, aortic insufficiency) had a low A-V index, and that mitral stenosis was associated with a high A-V index, it was only natural to wonder if there was any relationship between the A-V ratio and the electrical axis of the heart. This is a logical question because it had been shown that cases of the former type are associated with left axis deviation while those of the latter are associated with right axis deviation.

Weyler[8] studied a series of sixty-two cases with orthodiagrams and electrocardiograms made on the same day. The axis was determined by the method of Carter, Richter, and Greene.[9] He found, after statistical analysis of sixty-two cases, that there was a definite and direct correlation (by Pearson's coefficient of correlation; $r = +0.75$) between these two values. He showed that left axis deviation was associated with a low A-V ratio while right axis deviation was associated with a high A-V ratio. He concluded that if the A-V ratio expressed the ratio between the auricles and ventricles, then right axis deviation must be due to enlargement of the auricles and left axis deviation to enlargement of the ventricles.

In considering the vast amount of material written about axis deviation and the x-ray study of the heart, one is impressed with the variety of opinion and realizes the necessity of separating facts from theories, work based on sound principles from that lacking such a fundamental groundwork.

Factual work concerning axis deviation has demonstrated a definite relationship between preponderance of one or the other ventricle, when the heart is markedly enlarged, and axis deviation.[10-13] Likewise, it has been shown that position of the heart in the chest exerts some influence on the electrical axis.[11, 14-19] It is probable that other factors also exist which exert a similar influence. It is certain that axis deviation is dependent upon more than one factor; that two of these factors are ventricular preponderance and position of the heart.

Other work,[20] logical, but not yet based upon sufficient evidence, proposes abnormalities of the conducting system to be a large factor in the determination of the electrical axis.

Factual work concerning roentgenology of the heart is scarce. Several studies are based upon autopsy findings,[21, 22] but, in general, this work is founded upon clinical impressions.

It is the general opinion that x-ray examination is not of sufficient accuracy in the determination of relative ventricular preponderance to

be of clinical use, but that it serves its most useful purpose in determining gross enlargement. For this latter purpose, estimation of the area of the cardiac silhouette and comparison with tables based upon prediction formulas are considered the best procedure.[21, 23] Comparison of the various diameters is not so good for this purpose, but is better for measuring deviations from normal in the shape of the heart.[24]

In general, the term "normal" should be discarded and replaced by "average." A value above average does not necessarily signify abnormality, but merely indicates that the individual patient has a greater chance of being abnormal than one found to be within the "average" group.

PROCEDURE

General.—This work is based upon a study of 300 cases, unselected except for technical reasons. Each patient was examined clinically and fluoroscopically. Orthodiascopy, immediately preceded or followed by an electrocardiogram, was performed. The A-V ratio of the cardiac silhouette was then calculated and compared with the electrical axis of the electrocardiogram. The cases were divided into groups of clinically normal and abnormal, and from this the average normal values of the electrical axis were determined. The cases were then divided into three additional groups—normal, right axis deviation, and left axis deviation—and the results concerning the relationship of the A-V ratio to axis deviation were subjected to mathematical analysis.

Electrocardiographic Technique.—Carter and Greene[25] claimed that the electrocardiogram was the only satisfactory clinical method of estimating the relative preponderance of the two ventricles, and added that it was useful when combined with teleroentgenography to determine gross hypertrophy. They claimed the potential of the excitatory process to be important in determining the electrical axis. This factor was considered when using Einthoven's triangle, but was ignored in using the various formulas. They further stated that, for the accurate determination of the angle of the axis, the records in the different leads should be synchronized to avoid phasic variations between the several derivations, and that the measurements should be taken at identical periods in the respiratory cycle. However, it was admitted that these refinements were usually neither possible nor desirable except in physiologic experimentation of the greatest exactitude. As a routine, they recommended taking an average of the measurements of several peaks, to obtain a mean value of the angle independent of respiratory variation. Usually these measurements obey the Einthoven law ($E_1 + E_3 = E_2$), or else the error is so slight as to permit selection of a mean value of the angle. In a few cases where there was a marked discrepancy, the angle was determined from Leads I and III, Lead II being ignored. By this latter method the angle was accurate to within 5 degrees, and a greater degree of accuracy was thought to be unnecessary in ordinary clinical routine.

In the work of Weyler,[8] all cases were discarded in which the sum of Leads I and III did not equal Lead II. This is thought to be too exacting for work of this type.

In the majority of the cases in the present study, the tracings were in accord with Einthoven's law. In a few, there was a discrepancy of several millivolts and, in view of the above findings, these cases were included in the study. It was felt that otherwise the limitations would exceed the physical equipment, because to do physiologic work of great exactitude, a three-string galvanometer,

capable of taking three simultaneous leads, is necessary.[26] This study, therefore, is primarily clinical.

The axis was determined by the method of Carter, Richter, and Greene.[9] In cases showing variation in the amplitude of the QRS complexes, apparently due to the respiratory cycle, several consecutive complexes were measured and a mean value was found, as recommended by White and Boek[27] and Carter and Greene.[25]

No children under 5 years of age were included, and no tracings were included in which the maximal deflection was less than 5 millivolts because of the unreliability of the electrical axis in these circumstances.[28] Cases of delayed interventricular conduction were discarded because the estimation of axis deviation is valueless in the presence of this abnormality.

Summary of the limitations shows: (1) no patients under 5 years of age; (2) no cases of delayed interventricular conduction; (3) no cases in which the maximal amplitude of the QRS deflection was less than 5 millivolts.

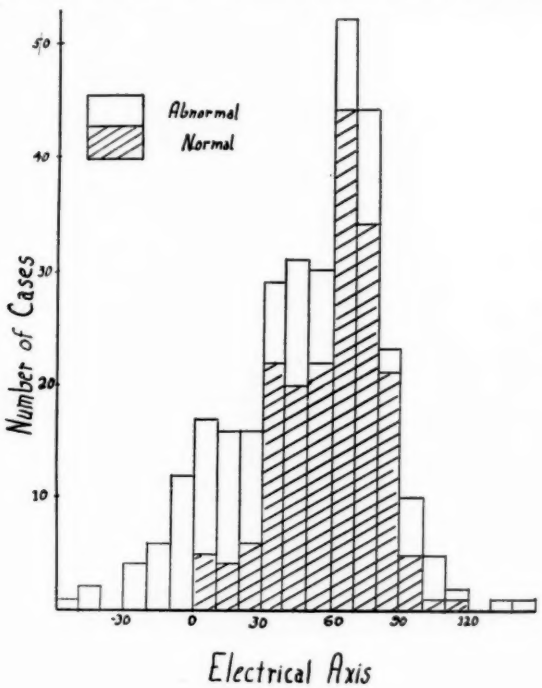

Fig. 2.

Determination of Average Normal Limits.—The 300 cases were divided into two groups, normal and abnormal, as determined by a thorough clinical examination (excluding the electrical axis). These were then charted (Fig. 2) according to the electrical axis. These values were analyzed,* and it was found that if a normal

*A Gram-Charlier frequency curve was fitted to the distribution of normal axis (y). From this it was computed that, if normal axis was defined as "y" from 20 to 90 degrees (less than 20, left axis deviation; more than 90, right axis deviation), more than 96 per cent of the clinically normal cases would fall in this range, subject to the condition, of course, that Fx represents the "true" distribution of "y."

Gram-Charlier frequency curve:

$$y = F(x') = \phi(x') + 0.0668\,\phi^3(x') - 0.0990\,\phi^4(x').$$

$\phi(x)$ represents the normal curve; $\phi^2(x)$ its first derivative; and so forth.

$$x' = \frac{x - \bar{x}}{\sigma x}$$

axis was considered to be from 20 to 90 degrees (as determined by Einthoven's triangle), 96 per cent of the normal patients would fall in this range.

In this work, for the purpose of mathematical analysis, the normal axis was considered to be from 20 to 90 degrees, values below 20 degrees indicating left axis deviation and values above 90 degrees indicating right axis deviation.

Roentgenologic Technique.—Fluoroscopy of the chest and heart was performed after the examiner's eyes were accommodated. All of the orthodiagrams were made by one operator, which eliminated the error due to the variation between the work of several different individuals. The orthodiagram was made with the patient standing and facing the operator, with the screen held fixed against the patient's chest. The tube was then moved around the cardiac and thoracic silhouettes and the tracing was made upon a glass plate held firmly in contact with the fluoroscopic screen by clamps. The tracing was later transferred to a piece of semitransparent paper from which the measurements were taken.

As recommended by Roesler,[29] the tracing was made during quiet respiration when the diaphragm was in its most cephalad position. Bardeen[21] recommended having the patient drink several glasses of water prior to the examination, swallowing all the air possible in order to form an air bubble in the stomach and facilitate visualization of the apex. This might be satisfactory in routine work, but could not be used here as it produced an elevation of the left dome of the diaphragm, causing a shift of the anatomic axis which, as will be shown later, would have affected all of the measurements under consideration in this study. The cardiac silhouette was traced during diastole, and the area of the great vessels during systolic contraction of the ventricles, thus obtaining the largest possible silhouette.

All cases in which pulmonary disease or other conditions precluded accurate determination of the cardiac silhouette were discarded.

The orthodiagram was measured in the usual manner (Fig. 1). The transverse diameter was taken to be the sum of *MR* (perpendicular from the midline to the most distant point on the right auricle) and *ML* (perpendicular from the midline to the most distant point on the left ventricle). The long diameter (*DG'*) was drawn from the auriculo-great-vessel junction on the right to the apex. Roesler[29] and others[2, 21, 30-33] considered the apex to be the furthermost point at the left lower pole. In the work of Levene and Reid,[5] the long diameter was drawn to the junction of the left ventricle and the diaphragm, which, plus the fact that their work was done with teleroentgenograms, explains to some extent the discrepancies between their results and the results of the present study.

A line (*D'G*) was drawn from the junction of the right auricle and the right dome of the diaphragm to the auriculoventricular junction on the left cardiac border. This line, according to some observers,[1, 2, 4, 5, 8] corresponds roughly to the position of the auriculoventricular septum. The A-V ratio was obtained by dividing the length of the long axis (*DG'*) above the point of bisection (*DX*) by the portion below this point (*XG'*).

The angle of inclination, or the anatomic axis, was taken to be the angle between the long axis and the horizontal, the measurement beginning at the left.

COMPARISON OF ORTHODIAGRAMS WITH TELEROENTGENOGRAMS

The purpose of this study is obvious. The work of Van Zwaluwenburg and Warren[2] was done by orthodiascopy, the apex being used as the lower pole of the longitudinal axis. The work of Levene and Reid[5] was based upon 7-foot plates and the lower pole of the long axis was taken to be the junction of the left ventricular shadow and the left dome of the diaphragm. The work of Weyler[8] was based upon orthodiagrams.

TABLE I

CASE NO.	AXIS (+)	TRANSVERSE DIAMETER						CARDIO-THORACIC RATIO			DIFFERENCE IN TRANSVERSE DIAMETER OF HEART, O AND N		DIFFERENCE IN TRANSVERSE DIAMETER OF HEART, N AND I		DIFFERENCE IN TRANSVERSE DIAMETER OF HEART, O AND I		ANGLE OF INCLINATION			DIFFERENCE IN ANGLE OF INCLINATION		LONG AXIS			A-V RATIO			DIFFERENCE IN A-V RATIO		
		HEART			THORAX																								
		O	N	I	O	N	I	O	N	I	CM.	%	CM.	%	CM.	%	O	N	I	O-N	N-I	O	N	I	O	N	I	O-N	N-I	O-I
14	47	10.7	12.0	11.9	20.9	25.2	26.2	51	48	45	1.3	12	0.1	1	1.2	11	45	37	43	8	6	12.0	12.7	13.0	.667	.649	.711	.018	.062	.044
117	60	12.6	13.8	13.2	23.2	26.0	28.0	54	53	47	1.2	10	0.6	4	0.6	4	44	23	27	21	4	13.4	13.2	13.5	.541	.885	.875	.344	.010	.334
110	60	10.9	12.0	11.5	20.8	24.0	26.3	52	50	49	1.1	10	0.5	4	0.6	5	46	38	40	8	2	13.1	13.0	13.6	.455	.368	.462	.087	.094	.007
100	63	11.7	12.8	12.7	22.5	25.4	27.5	52	50	46	1.1	10	0.1	1	1.0	8	44	37	40	7	3	13.3	14.2	14.3	.705	.378	.589	.327	.211	.116
33	65	9.8	10.3	9.5	20.9	24.3	26.5	47	42	36	0.5	5	0.8	6	-0.3*	-3*	49	34	43	15	9	12.0	11.4	13.7	1.000	.964	1.015	.046	.051	.015
86	65	10.2	11.8	11.4	22.4	26.4	28.0	46	45	41	1.6	16	0.4	3	1.2	12	44	31	38	13	7	11.6	12.3	12.6	.634	.781	.680	.147	.101	.046
119	68	9.4	9.9	9.6	22.0	25.5	25.8	42	39	37	0.5	5	0.3	3	0.2	2	52	49	53	3	4	10.8	11.8	12.6	1.000	.965	1.062	.035	.097	.062
120	70	11.0	12.7	11.5	21.8	25.0	26.0	50	51	46	1.7	16	1.2	9	0.5	4	43	33	46	10	13	12.0	12.8	12.8	.621	.541	.778	.080	.237	.157
17	73	10.4	10.9	10.9	21.8	25.2	25.7	48	43	42	0.5	5	0	0	0.5	5	53	46	48	7	2	12.9	13.2	13.4	.896	.782	.786	.114	.004	.110
79	75	12.9	14.0	12.7	24.0	27.8	28.4	54	50	45	1.1	8	1.3	9	-0.2*	-1*	41	25	39	6	14	13.1	13.8	14.0	.523	.604	.750	.081	.146	.027
32	80	10.5	12.0	11.1	21.4	24.7	26.2	49	48	42	1.5	14	0.9	8	0.6	6	42	32	38	10	6	11.9	11.9	12.0	.482	.564	.500	.082	.064	.018
105	80	9.9	10.7	10.5	21.2	24.3	26.0	47	44	40	0.8	8	0.2	2	0.6	6	48	45	48	3	3	12.4	13.2	13.5	.746	.713	.558	.033	.155	.188
123	90	10.9	11.7	11.4	21.2	25.3	25.6	51	46	44	0.8	8	0.3	3	0.5	4	53	42	48	11	6	12.4	13.4	13.1	.771	.696	.770	.075	.074	.001
92	102	9.2	10.1	9.9	23.2	26.1	28.2	40	39	35	0.9	10	0.2	2	0.7	8	59	46	53	13	7	13.0	13.0	14.2	.912	.805	.944	.107	.139	.032
31	113	11.7	13.5	12.7	24.4	26.8	27.2	48	50	47	1.8	15	0.8	6	1.0	8	44	36	41	8	5	13.0	14.7	14.5	.529	.632	.727	.103	.095	.198

O = Orthodiagram.
N = 7-foot plate (quiet respiration).
I = 7-foot plate (inspiration).
*See text.

Several workers[23, 34] have reported the average magnification of the cardiac shadow on a 7-foot plate. Their results were variable. It was desired to determine: (1) the amount of magnification obtained in our clinic; (2) the effect of the respiratory phase in a series of cases; and (3) the effect, if any, of these factors on the A-V index.

The work of Hodges[34] was done with the patient seated in front of a piece of apparatus which permitted centering of the patient under fluoroscopic visualization, followed by a 7-foot plate and orthodiascopy without any change in position on the part of the patient. These conditions were as nearly ideal as could be hoped for in a problem of this type, and the results, expressed in percentage relations between cardiac silhouette areas, are definite and authoritative.

The present series of fifteen normal persons were subjected to electrocardiography, orthodiascopy, and teleroentgenography, the examinations taking place in succession and as rapidly as routine work permitted. There were two 7-foot plates taken of the chest; one taken with the usual chest technique, i.e., with the patient holding the breath in deep inspiration, and the other taken during quiet respiration in an attempt to simulate the conditions obtained during orthodiagraphy.

TABLE II

DIFFERENCE BETWEEN	MINIMAL	MAXIMAL	AVERAGE
Transverse diameter:			
O and N	0.5 cm.	1.8 cm.	1.1 (1.09) cm.
	5%	16%	10 (10.1) %
N and I	0	1.3 cm.	0.5 (0.51) cm.
	0	9%	4 (4.06) %
O and I	0.2 cm.	1.2 cm.	0.7 (0.707) cm.
	2%	12%	6 (6.3) %
	-0.2 cm.	-0.3 cm.	-0.25 cm.
	-1%	-3%	-2%
Angle of inclination:			
O and N	3°	21°	10 (9.53)°
N and I	2°	14°	6 (6.06)°
A-V index:			
O and N	.018	.344	.112
N and I	.004	.237	.103
O and I	.001	.334	.090

Again, with consideration of the technical flaws in this procedure, it was nevertheless believed to give pertinent and presentable data because (1) the technique was the same as in the usual routine examination and (2) the results were consistent regarding changes in the transverse diameter of the heart, the transverse diameter of the thorax, the cardiothoracic ratio, and the angle of inclination (anatomic) of the heart with the horizontal.

The results of the examinations in these fifteen cases are seen in Table I. The study of the transverse diameter of the heart, with a comparison of the values obtained by the different methods, is of primary importance.

In comparing the values, it was found that, without exception, those obtained by the 7-foot plate during quiet respiration exceeded those obtained by orthodiascopy. As shown in Table II, the maximal difference was 1.8 cm. (16 per cent), and the minimal 0.5 cm. (5 per cent), with an average of 1.1 cm. (10 per cent). These figures are valuable in that they demonstrate the results obtained in this clinic to be (1) consistent and (2) comparable with findings obtained elsewhere.

In comparing the values of the transverse diameter of the heart as obtained by the 7-foot plates, the variable being the respiratory phase, it was found that the values obtained during quiet respiration exceeded those obtained during forced inspiration with but one exception.* The minimal decrease was zero; the maximal 1.3 cm. (9 per cent). The average decrease was 0.5 cm. (4 per cent). It may be positively stated that no value obtained during quiet respiration was less than any value obtained at the end of inspiration. This was easily explained by the fact that a high diaphragm (present during quiet respiration) tends to produce a transverse position of the heart, while a low diaphragm (present with deep inspiration) tends to make the heart assume a vertical position.

The difference in the values of the transverse diameter obtained by orthodiagraphy and teleroentgenography (plate taken during inspiration) are valuable from a practical standpoint; i.e., the latter method is the routine technique for taking chest plates in most laboratories and much work in regard to cardiac mensuration is based upon such plates. The values obtained by the use of the 7-foot films were greater than those of the orthodiagrams, with but two exceptions. These exceptions may be explained when the great number of variable factors involved are considered, the two foremost factors being the magnification of the plate over the orthodiagram and the decrease in the transverse diameter with inspiration. Other factors to be considered are depth of respiration, etc. The maximal difference was 1.2 cm. (12 per cent); the minimal, 0.2 cm. (2 per cent); the average, 0.7 cm. (6 per cent).†

The angle of inclination made by the long axis of the heart with the horizontal was, in all cases, smaller in the teleroentgenogram (normal respiration) than in the orthodiagram. The maximal difference was 21°; the minimal, 3°; the average, 10°. The value of the angle between quiet respiration and deep inspiration likewise showed consistent results, all of the latter being greater than the former. The maximal difference was 14°; the minimal, 2°; the average, 6°.

The former comparison (between the angle on the orthodiagram and 7-foot plate) is not valid because, in the former, the apex is used as the

*This was a case in which the changes were minimal in all of the observations. It is assumed that the patient did not use the diaphragm to full advantage in the act of respiration.

†These values were calculated by considering only the thirteen positive values. The two negative values of 0.2 and 0.3 cm. averaged 0.25 cm.

lower pole of the axis, while in the latter, the junction of the left ventricle with the diaphragm is utilized for this purpose. The comparison is included only for its practical interest. On the other hand, the comparison of the two films is between two values which differ only in the phase of respiration. These figures are of definite value.

The long axis will be mentioned here merely as a preliminary to a study of the A-V index. This value (L) is subject to the same criticism as is presented in the preceding paragraph. It will be noted that, as this subject is being developed from the simple to the complex (i.e., from an initial study of transverse diameter to a final consideration of the A-V index), the number of conditioning factors becomes multiplied with each step. The long axis, with five exceptions, is greater in the normal teleroentgenogram than in the orthodiagram, and still greater in the teleroentgenogram taken during forced inspiration. These five exceptions are minor and are not consistent in regard to the type of case affected (i.e., transverse or vertical heart, high diaphragm, etc.) and serve to bring out the multitude of further conditioning factors involved. Some of the factors are the magnification due to the 7-foot plate, change in the anatomic angle with respiration, and, of maximum importance, difference in the selection of the lower pole of the cardiac long axis.

The A-V index as computed from the film taken during quiet respiration was smaller than the value computed from the orthodiagram, with five exceptions. The minimal variation was 0.018; the maximal, 0.344; and the average, 0.112.

The effect of respiration upon the A-V index was somewhat less. A comparison of the values as computed during quiet respiration and at the end of forced inspiration (both films) showed that the values of the latter were greater than those of the former, with four exceptions. The minimal variation was 0.004; the maximal was 0.237; and the average, 0.103.

A comparison of the values of the A-V index as computed from the orthodiagram and the film taken during forced inspiration shows that the values of the former are less than those of the latter, with four exceptions. The minimal variation was 0.001; the maximal was 0.334; and the average, 0.090.

The exceptions in the three preceding paragraphs did not all occur in the same four or five cases, but were distributed through nine cases, giving a disagreement in nine of fifteen cases. Furthermore, it should be noted that Cases 117 and 100 show differences of 0.344 and 0.327, respectively, between the A-V ratios as determined by the orthodiagram and the film during quiet respiration. Case 117 shows a difference of 0.334 between the value obtained by the orthodiagram and that obtained by the film during inspiration. These three values are in excess of the *range* of normality (0.300) as expressed by Levene and Reid,[5] who accepted 0.500 to 0.800 as the limits of normal.

It was considered unnecessary to submit these results to statistical analysis because, as shown above, it was evident that the changes were consistent in the case of all the values except the A-V index.

The results of this study suggest that: (1) with the exception of the A-V index, most of the usual cardiac measurements show differences due to technique which can be predicted and are, more or less, constant; (2) results obtained by one technique are comparable only with other results obtained by the use of the same technique; (3) the A-V index is unreliable as a cardiac measurement.

RESULTS

The 300 cases were divided into two groups, normal and abnormal, according to clinical findings. The electrical axis and the A-V index for each case were recorded in Table III. A scatter diagram (Fig. 3) based upon these results is presented. A high degree of correlation, if present, would tend to cause the dots to approach a straight line. Such is not the case in this instance, as the dots are widely scattered.

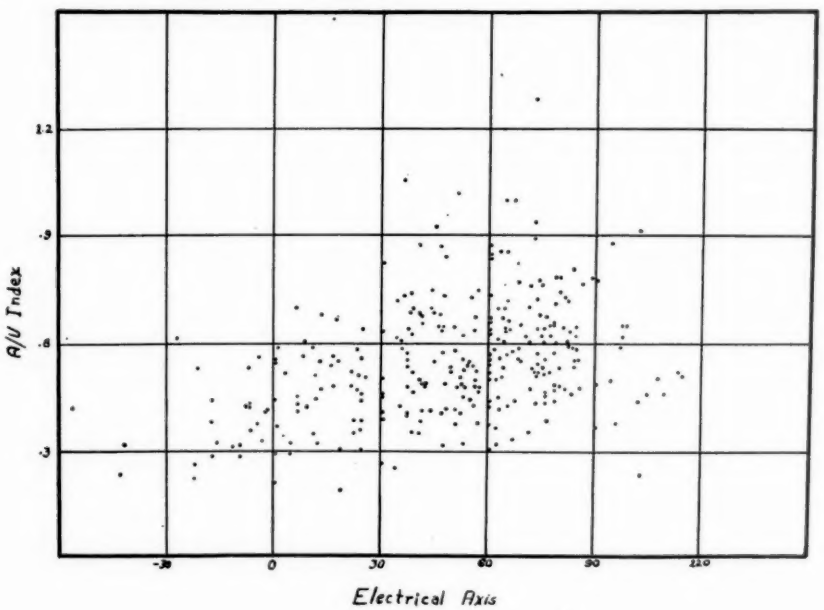

Fig. 3.

The results were subjected to statistical analysis. The cases were divided into the following groups, and the correlation between the axis and the A-V index was determined for each group:

1. Normal clinically; no significant correlation.
2. Abnormal clinically; $r = 0.400$.
3. Left axis deviation; no significant correlation.
4. Right axis deviation; no significant correlation.
5. Normal axis; $r = 0.303$.

TABLE III

NO.	AXIS	A-V	NO.	AXIS	A-V
Clinically Normal Cases					
1	75	0.688	59	72	0.541
2	23	0.472	60	37	0.531
3	76	0.600	61	77	0.397
4	79	0.792	62	62	0.500
5	73	0.522	63	97	0.652
6	65	0.601	64	39	0.734
7	73	0.535	65	66	0.326
8	49	0.531	66	7	0.458
9	47	0.481	67	56	0.552
10	60	0.303	68	79	0.577
11	73	0.641	69	16	0.569
12	25	0.516	70	38	0.731
13	63	0.867	71	85	0.542
14	47	0.667	72	49	0.732
15	50	0.581	73	65	0.802
16	44	0.697	74	60	0.739
17	73	0.896	75	83	0.605
18	75	0.613	76	56	0.444
19	84	0.461	77	57	0.487
20	42	0.493	78	30	0.505
21	57	0.737	79	75	0.523
22	30	0.462	80	85	0.624
23	47	0.631	81	35	0.612
24	57	0.543	82	40	0.693
25	17	0.541	83	36	0.423
26	65	0.702	84	97	0.614
27	87	0.772	85	69	0.593
28	65	0.641	86	65	0.634
29	66	0.638	87	52	0.408
30	39	0.615	88	58	0.530
31	113	0.529	89	64	0.661
32	80	0.482	90	65	0.728
33	65	1.000	91	25	0.439
34	75	0.769	92	102	0.912
35	79	0.600	93	82	0.477
36	60	0.836	94	56	0.486
37	79	0.711	95	49	0.549
38	36	0.601	96	60	0.652
39	78	0.662	97	85	0.589
40	60	0.549	98	76	0.569
41	85	0.564	99	50	0.378
42	68	0.771	100	63	0.705
43	63	0.865	101	75	0.544
44	57	0.475	102	30	0.398
45	60	0.500	103	57	0.628
46	45	0.927	104	52	0.511
47	69	0.645	105	80	0.746
48	84	0.630	106	78	0.561
49	54	0.545	107	80	0.540
50	77	0.528	108	78	0.654
51	53	0.538	109	37	0.482
52	73	0.526	110	60	0.455
53	60	0.671	111	65	0.574
54	39	0.701	112	74	0.434
55	7	0.704	113	79	0.455
56	45	0.555	114	81	0.648
57	44	0.416	115	80	0.786
58	84	0.591	116	38	0.355

TABLE III—CONT'D

NO.	AXIS	A-V	NO.	AXIS	A-V
117	60	0.541	152	87	0.477
118	63	0.605	153	37	0.573
119	68	1.000	154	62	0.871
120	70	0.621	155	7	0.434
121	53	0.324	156	37	0.400
122	63	0.563	157	63	0.421
123	90	0.771	158	71	0.352
124	72	0.488	159	60	0.434
125	36	0.588	160	63	0.466
126	65	0.426	161	90	0.493
127	69	0.565	162	54	0.563
128	57	0.500	163	55	0.456
129	47	0.884	164	30	0.632
130	25	0.640	165	41	0.417
131	60	0.636	166	24	0.591
132	60	0.662	167	52	0.493
133	36	1.059	168	74	0.725
134	57	0.674	169	71	0.702
135	60	0.573	170	49	0.494
136	90	0.772	171	13	0.563
137	72	0.761	172	30	0.272
138	60	0.887	173	40	0.352
139	83	0.597	174	25	0.456
140	85	0.646	175	67	0.588
141	43	0.700	176	42	0.493
142	4	0.529	177	76	0.453
143	41	0.659	178	87	0.402
144	69	0.563	179	39	0.464
145	83	0.716	180	38	0.638
146	62	0.586	181	67	0.448
147	71	0.600	288	19	0.186
148	75	0.641	289	79	0.495
149	40	0.696	290	84	0.808
150	54	0.621	299	38	0.512
151	1	0.588			
		Clinically Abnormal Cases			
182	48	0.421	205	77	0.684
183	21	0.489	206	74	1.272
184	50	0.420	207	98	0.651
185	25	0.353	208	23	0.343
186	56	0.726	209	12	0.452
187	102	0.448	210	47	0.411
188	-8	0.434	211	62	0.806
189	114	0.519	212	7	0.414
190	0	0.567	213	-12	0.306
191	-17	0.389	214	9	0.431
192	-10	0.312	215	9	0.600
193	19	0.665	216	-6	0.540
194	53	0.463	217	74	0.591
195	35	0.265	218	42	0.494
196	57	0.382	219	25	0.561
197	-22	0.231	220	5	0.296
198	30	0.458	221	58	0.488
199	65	0.532	222	48	0.851
200	-1	0.426	223	5	0.327
201	30	0.824	224	8	0.562
202	0	0.291	225	48	0.290
203	40	0.500	226	20	0.270
204	-16	0.287	227	-3	0.333

TABLE III—CONT'D

NO.	AXIS	A-V	NO.	AXIS	A-V
228	13	0.475	263	47	0.323
229	-26	0.611	264	-17	0.450
230	50	0.649	265	-7	0.423
231	13	0.684	266	38	0.558
232	46	0.688	267	46	0.659
233	-19	0.300	268	145	0.594
234	62	0.319	269	21	0.524
235	2	0.369	270	-21	0.541
236	-41	0.321	271	-56	0.433
237	-5	0.391	272	79	0.481
238	51	1.023	273	78	0.615
239	10	0.590	274	0	0.209
240	11	0.353	275	-7	0.437
241	36	0.724	276	0	0.562
242	108	0.504	277	94	0.883
243	63	0.612	278	63	0.667
244	60	0.518	279	60	0.622
245	-43	0.236	280	27	0.510
246	109	0.462	281	96	0.380
247	77	0.650	282	90	0.370
248	0	0.446	283	11	0.516
249	73	0.932	284	60	0.379
250	74	0.773	285	18	0.555
251	23	0.387	286	44	0.753
252	51	0.488	287	30	0.414
253	41	0.386	291	104	0.463
254	-22	0.267	292	86	0.568
255	-10	0.298	293	-3	0.581
256	-1	0.426	294	38	0.698
257	25	0.389	295	130	0.722
258	12	0.322	296	96	0.591
259	-16	0.318	297	81	0.739
260	25	0.304	298	76	0.469
261	73	0.466	300	17	0.489
262	-6	0.363			

6. Normal axis and normal clinically; no significant correlation.

7. Normal axis and abnormal clinically; $r = 0.630$.

Groups 2, 5, and 7, taken together, show that there is a true correlation of fairly high magnitude between the electrical axis and the A-V index in the group of abnormal cases with a normal electrical axis. The correlations shown in Groups 2 and 5 are results of the fairly high correlation found in Group 7 where the variables are classified in the above manner. Group 5 is only a real correlation inasmuch as it reflects Group 7, since clinically normal and abnormal cases are not statistically homogeneous* and there is no legitimate reason for combining them.

*The clinically normal cases showed a mean A-V index of 0.589 and a mean axis of 58.903. The clinically abnormal cases showed a mean A-V index of 0.504 and a mean axis of 53.770. The means were found to be significantly different:

A-V index	$D = 0.085$	$\sigma D = 0.02041$
Axis	$D = 25.133$	$\sigma D = 4.0395$

(D = difference between the respective means; σD is a measure which shows the range of probability of getting the measure D as a result of pure chance. When any measure is greater than 3.5 or 4.0 times its own standard deviation (σ), it is said to be significant; i.e., the probability that this measure will occur as a result of pure chance in picking the sample is very small.)

This shows the clinically normal cases to be different with respect to the two measures (axis and A-V index) under consideration than the clinically abnormal cases.

Conclusion (Statistical).—There exists a fairly high, valid correlation between the electrical axis and the A-V index in the group of cases that are clinically abnormal with normal electrical axes ($r = 0.630$). There is no significant correlation between the electrical axis and the A-V index in any of the other classes.

DISCUSSION

The largest A-V ratio encountered by Van Zwaluwenburg[3] was 1.42 (in a case of mitral stenosis); the smallest, 0.25 (in a case of aortic regurgitation). In the present study, none were encountered as great as 1.42, but there were four ratios less than 0.25.* Case 288 was a young woman, perfectly normal except for obesity. The chest was of the short, thick type, and the diaphragm was high, which caused the heart to lie in an extreme transverse position. The electrical axis was 19°. The blood pressure was within normal limits, as were the findings in the remainder of the physical examination. Case 197 was a 65-year-old man with hypertensive and arteriosclerotic heart disease. Case 245 was a 35-year-old man with clinical and electro cardiographic evidence of a recent anterior coronary occlusion, whose orthodiagram was that of a normal transverse heart. Case 274 was a 57-year-old man with evidence of an old coronary occlusion and enlargement of the left ventricle on the basis of arteriosclerosis and hypertension. The above cases do not constitute sufficient evidence upon which to base any conclusions; they are presented only for completeness.

It is noteworthy that the cases presented by Van Zwaluwenburg gave, in general, higher values for the A-V index than the cases studied in this present work. Van Zwaluwenburg stated the normal *limits* of the A-V index to be 0.534 and 0.704. In the present work, the *mean* value of the normal cases was 0.589, which is very close to Van Zwaluwenburg's lower limit of normal. This fact is difficult to explain because both studies were based upon the orthodiagram, and, in both instances, the long axis was drawn to the apex. Van Zwaluwenburg did not mention the number of cases in his series. If this was small, it would limit the value of the study and explain, at least partially, the difference between his results and the results of this study.

Van Zwaluwenburg and Warren[2] claimed that every case of mitral stenosis gave a value for the A-V index above 0.880, even when the stenosis was complicated by regurgitation. In the present study, there were sixteen cases of definite mitral stenosis.† Of these, ten were complicated by mitral regurgitation; two by aortic regurgitation; and two by aortic stenosis. Only two of the sixteen cases gave an A-V index of more than 0.880, and both of these were complicated by mitral regurgitation. The two lowest values were 0.382 and 0.389, found in cases

*Case 288 = 0.186; Case 197 = 0.231; Case 245 = 0.236; Case 274 = 0.209.

†Cases 186, 187, 191, 196, 207, 211, 221, 222, 232, 238, 242, 261, 273, 277, 279, and 294.

complicated by aortic stenosis and regurgitation, respectively. The average value of the A-V index for the sixteen cases of mitral stenosis was 0.646.

On the other hand, there were eleven definitely normal cases* with A-V indices above 0.800, eight of them being above 0.880. All of these were normal hearts of the vertical type, i.e., in a person with a long, narrow chest. This should make one extremely cautious in using the A-V index as a method for the diagnosis of early mitral stenosis, as recommended by Reid and Levene.[7]

The work of Weyler[8] was based upon orthodiagrams made by several different operators. This introduced the factor of personal technique, which, however, should produce but slight differences in the various measurements. However, his work is open to criticism concerning the total number of cases. A series of sixty-two cases is too small a number from which to expect valid conclusions from statistical analysis.

SUMMARY AND CONCLUSIONS

A study was made of the A-V index of the cardiac silhouette as to its nature, its general usefulness, and, specifically, its relationship to the axis of the electrocardiogram.

The data concerning the A-V index and the electrical axis in 300 unselected cases were subjected to mathematical analysis. The cases were separated into two clinical groups, normal and abnormal, and the average limits of the normal electrical axis determined. Fifteen normal subjects were studied, in addition to the above procedures, by the means of two teleroentgenograms, one taken during quiet respiration and the other after deep inspiration. The values so obtained were studied to determine the relationship of the various cardiac measurements as obtained by the different techniques.

The following conclusions were reached:

1. In general, there is no valid correlation between the A-V index and the electrical axis of the heart. The A-V index is of no clinical importance and bears no definite relationship to mitral stenosis, and is neither reliable nor consistent as a cardiac measurement.

2. The limits of normal in regard to the electrical axis of the heart should not be used dogmatically. An abnormal value does not always mean an abnormal heart, but merely indicates that the possibility of the heart's being abnormal is greater than in a case with a normal value for the axis.

3. As determined by statistical methods, 20 to 90° (Einthoven's triangle) is the most satisfactory average normal range for the electrical axis.

*Cases 13, 17, 33, 43, 46, 73, 92, 119, 129, 138, and 154.

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LIVEDO RETICULARIS: A PERIPHERAL ARTERIOLAR DISEASE

NELSON W. BARKER, M.D.,* EDGAR A. HINES, JR., M.D.,* AND
WINCHELL McK. CRAIG, M.D.†
ROCHESTER, MINN.

LIVEDO reticularis is a term which has been used to describe a local circulatory disorder characterized by a mottled, blotchy or reticular, bluish discoloration of the skin. There is usually subjective and objective coldness of the skin, and the color of the blotches may vary from rather deep blue when the patient is in a cold environment, to red or reddish purple when he is in a warm environment. The condition has also been described under the terms "livedo racemosa," "livedo annularis," and "asphyxia reticularis." The literature on the subject is somewhat confusing, but good descriptions and discussions have been given by Adamson,[1] Williams and Goodman,[2] Beeker,[3] and Ebert.[4] The term "livedo reticularis" seems to have superseded the other terms in recent years.

Williams and Goodman have divided cases of livedo reticularis into three groups, namely, (1) cutis marmorata, a rather commonly observed mottling of the skin on exposure to cold which disappears when the patient is brought into a warm environment, and seems to be unassociated with any other disease; (2) livedo reticularis idiopathica, in which the bluish mottling is more intense and persists in spite of changes of temperature, although there may be variations in the mottling; in this group there is no evidence of any associated disease; in most of the cases which Williams and Goodman[2] place in this category the patients were children, and many had congenital defects elsewhere in the body; and (3) livedo reticularis symptomatica, in which the mottling is also persistent; in this group there is evidence of some other disease which affects the cutaneous and subcutaneous vascular system. In this category have been placed livedo reticularis associated with the erythema induratum type of tuberculids of the lower extremities, which was described by Adamson,[1] and those cases in which it was associated with syphilis, as described by Ehremann.[5] In these two groups definite inflammatory changes have been demonstrated in the arterioles of the subcutaneous tissue. Recently, Ketron and Bernstein[6] described a case, with necropsy studies, in which extensive livedo reticularis was associated with periarteritis nodosa.

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*From the Division of Medicine, The Mayo Clinic.
†From the Section on Neurologic Surgery, The Mayo Clinic.

In 1922, Stokes[7] described a case of typical livedo racemosa (livedo reticularis) which had first appeared when the patient was 27 years old. There was no evidence of tuberculosis or syphilis, but biopsy revealed obliteration of some of the larger arterioles. A similar case was described by Becker,[3] who found perivascular lymphatic infiltration and adventitial fibrosis, in addition to the intimal proliferation. In another case described by Becker, biopsy of the skin showed very few changes

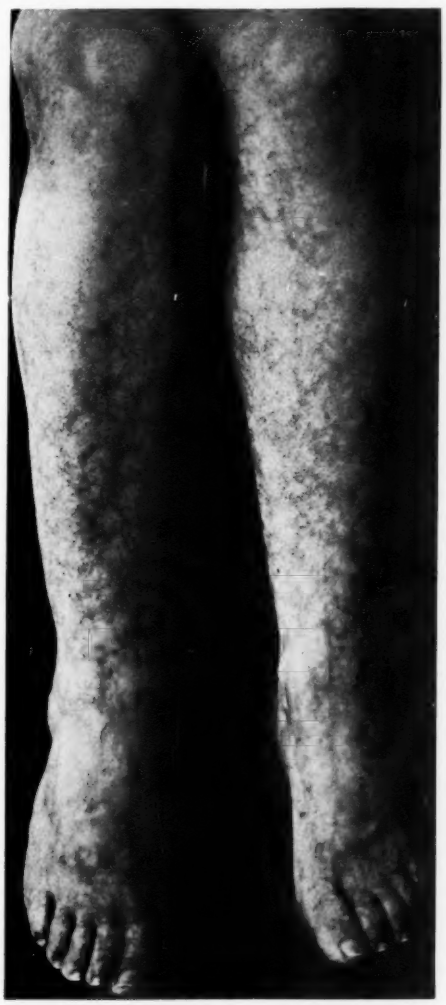

Fig. 1.—Case 11. Uncomplicated livedo reticularis, showing typical mottling and the usual involvement of feet and legs to knees.

other than a slight lymphocytic periarteriolar infiltration. This patient had hypertension and hyperthyroidism with an adenomatous goiter. The influence of these conditions as an etiological factor is doubtful. Ebert[4] reported a case of extensive livedo reticularis, associated with

recurrent ulcerating nodules of the legs. Biopsy revealed marked inflammatory changes in the arterioles and small arteries, with perivascular lymphocytic infiltration, intimal proliferation, and thrombosis of some of the small veins. Ebert considered his case as one of permanent livedo reticularis, probably associated with tuberculids. However, he was not able to find other evidence of tuberculosis; the histologic changes were not entirely typical of tuberculid; and the tuberculin reaction of the skin was negative. Ebert himself questioned whether true tuberculosis was the etiological factor.

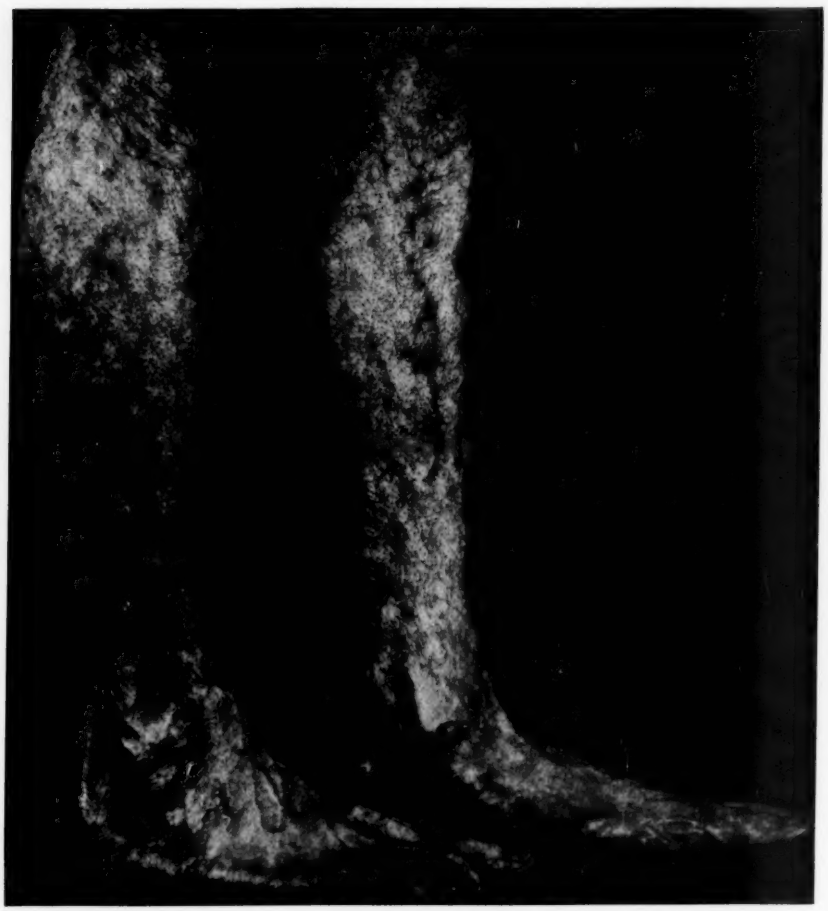

Fig. 2.—Case 4. Livedo reticularis with necrotic ulcers of right leg.

It is probable that livedo reticularis should not be considered as a disease entity, but rather as a circulatory phenomenon. It is also probable that the physiologic disturbance which manifests itself as livedo reticularis may be produced by different diseases, some known and some unknown, just as Raynaud's phenomenon may occur as the result of

cervical rib, thromboangiitis obliterans, or scleroderma, or may occur in the absence of any of these diseases and be called simply Raynaud's disease.

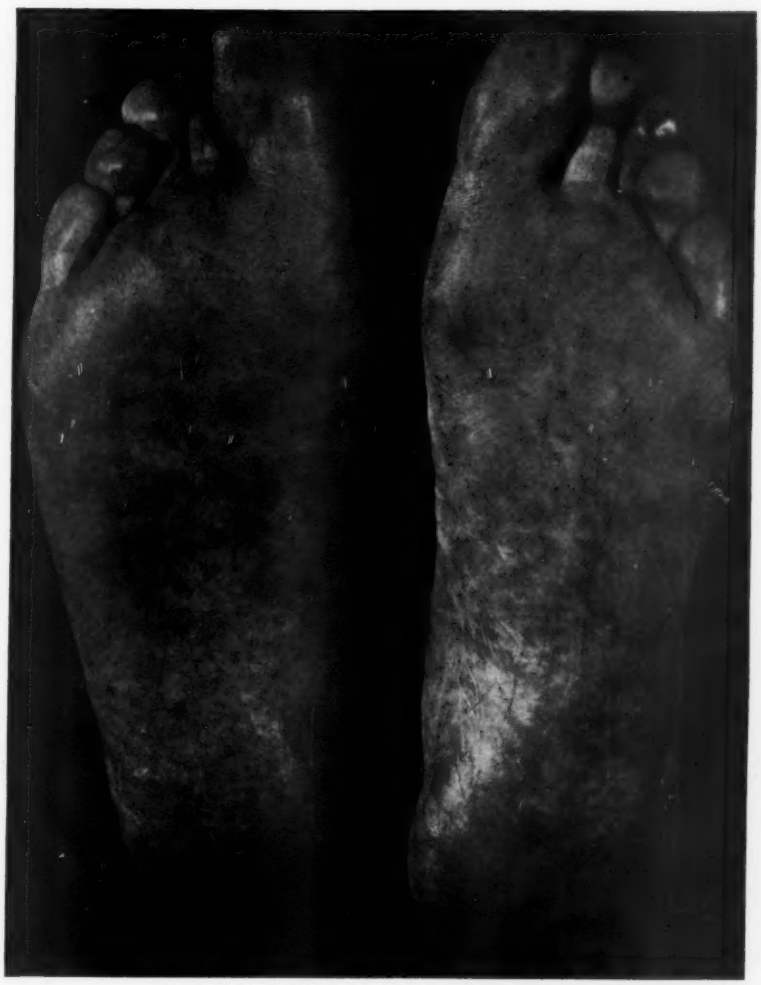

Fig. 3.—Case 2. Livedo reticularis with gangrene of distal half of right second toe and healed gangrene of skin of left third toe.

We wish to report a series of thirteen cases of livedo reticularis. All of these patients had a persistent bluish to bluish-red mottling of the skin of both legs and feet (Fig. 1). In some instances this mottling extended also to the thighs; it involved the hands and arms to a less degree, and even the lower part of the trunk. The livedo was more noticeable when the patients were exposed to cold, and there was a persistently lowered temperature of the skin. The age at onset varied from 21 to 47 years. There was no evidence of syphilis, tuberculosis, or tuberculids in any of the cases. Also, there was no evidence of occlusive

TABLE I

DATA ON CASES OF LIVEDO RETICULARIS

CASE NO.	AGE (YR.)	SEX	EXTENT OF LIVEDO RETICULARIS	DURATION OF LIVEDO RETICULARIS (YR.)	GANGRENE, ULCERATION, OR ARTERIAL OCCLUSIONS	SUBJECTIVE SYMPTOMS	BLOOD PRESSURE ON ADMISSION (MM. OF MERCURY)	ASSOCIATED CONDITIONS
1*†	34	M	Progressively, legs, feet, thighs, arms, and lower part of trunk	8	Recurrent painful ulcers of legs, intractable to treatment; acute arterial occlusions of both first toes, without gangrene	Coldness, numbness, paresthesias; severe pains in ulcers and in first toes at time of arterial occlusion	115/64	Questionable lead poisoning at onset, not confirmed later; peripheral neuritis, nervous instability, anxiety neurosis, and narcotic addiction
2†	34	M	Legs and lower part of thighs	1	Two attacks of superficial gangrene, distal half of right second toe	Cold feet; severe pain in gangrenous toe	135/85	Frost bite five years before onset; severe sore throat at onset of livedo
3	31	M	Progressively, feet, legs, hands, and left arm	3	Five attacks of superficial gangrene of toes, R2 (twice), R4, L3, L4	Coldness; severe pain in gangrenous toes for two to three months	125/85	Gangrene usually preceded by mild trauma
4	25	M	Both feet and legs below knees	4	Recurrent ulcers of lower legs, usually after injury	Coldness; mild to moderate pain in ulcers	114/76	Lead found in urine

*This case has been reported previously in detail.[8]

†Sympathetic ganglionectomy was performed in these cases.

5†	39	M	Both feet and legs below knees	2	Gangrene and amputation R2 toe, gangrenous ulcer R1 toe, ulcer lateral aspect right foot	Marked coldness of feet and legs, with aching, in cold weather; severe pain in gangrenous toes and ulcer	200/130	Labile blood pressure; minimal retinal arteriosclerosis; pains in ankles and wrists, with some swelling
6	37	F	Both feet and legs to knees, few areas on arms	14	One small ulcer lower leg	Coldness, aching, swelling in hot weather	124/78	Obesity
7	46	F	Both legs to mid-thighs, both arms above elbows	Uncertain	0	Slight swelling of ankles	116/78	Hypertension twice during toxemias of pregnancy; two cerebral vascular accidents
8	35	M	Both feet and legs to knees	4	0	0	156/104	Cerebral vascular accident, with hemiplegia
9	47	M	Both feet and legs to knees	1	0	Coldness, aching, burning, numbness	160/102	Arsenic found in urine; peripheral neuritis, nervous instability, anxiety neurosis
10	50	F	Progressively, both feet, legs, thighs, lower part of abdomen, left arm	6	0	Coldness, aching especially when dependent; relief with heat and elevation	150/90	Positive tourniquet test, no abnormalities of the blood
11	37	F	Both feet and legs to knees	Uncertain	0	Coldness, aching, numbness	126/75	Menopause, nervous instability
12	56	F	Both feet and legs to knees	30?	0	Slight aching	170/114	Brain tumor (meningioma)
13	40	F	Both feet and legs to knees	4	0	Coldness	158/110	Carcinoma of breast, nervous instability

disease of the larger arteries such as the dorsalis pedis, posterior tibial, and popliteal arteries, and there were no varicose veins or clinical features of ordinary venous insufficiency. The essential data in these cases are given in Table I.

In addition to the livedo, recurring ulceration of the skin of the legs, which, the patients felt, began as an intensification of an area of bluish discoloration, had developed in three cases (Fig. 2). In two of the three cases the ulcers were very resistant to treatment, and in all three they were very painful. In the case in which there was the most extensive ulceration, occlusion of the arteries of each great toe also developed on separate occasions. This was characterized by sudden pain, pallor, and marked decrease in skin temperature which persisted for several weeks. In three other cases there was a peculiar type of gangrene of the skin of the toes, characterized by a fairly sudden onset of purplish-black discoloration and moderately severe pain which persisted for several weeks or months and involved the distal half to the entire toe (Fig. 3). In each instance the skin ultimately became black and hard and finally sloughed, with healing except in one case in which it was necessary to amputate the toe because of nonhealing and severe pain.

COMMENT

Etiology.—We were unable to demonstrate a common etiological factor in our group of cases. Of the thirteen patients, six were women and seven were men. It is interesting, however, that, of the six cases of ulceration and gangrene, five occurred in men, and the one that occurred in the woman was a comparatively small, benign ulcer. All but one of the men were mild to moderate smokers. All but one of the women were nonsmokers. All but one (a man, Case 3) who had ulceration or gangrene were smokers. In four of the thirteen cases there was moderate hypertension, and, in one other case, there was a history that hypertension had occurred twice in association with toxemias of pregnancy. In this case and in one other in which there was hypertension, cerebral vascular accidents had occurred at relatively early ages (35 and 38 years). In a few other cases in the literature, livedo reticularis has been observed in association with hypertension, arteriosclerosis, and heart disease. However, it is probable that these vascular disorders are coincidental, rather than etiological factors. They may indicate a tendency toward vulnerability of the vascular system as a whole.

In one of our cases there was a history of exposure to arsenic, and arsenic was found in the urine. One patient had an indefinite history of lead poisoning at the onset of the livedo, but no lead was found in the urine at the time of our examination. Another patient had no history of lead poisoning, but lead was found in the urine at the time of our examination. In three other cases the urine was examined for lead, but the results of examination were negative. One patient had a his-

tory of severe sore throat at the time of the onset of the livedo; four patients had marked nervous instability; and two patients had definite peripheral neuritis (confirmed by pathologic studies in one case), but in these instances it is probable that the neuritis was the result of the underlying vascular disease or an associated phenomenon, rather than a definite etiological factor. Results of serologic tests of the blood for syphilis were negative in all cases. Roentgenograms of the chest were negative for evidence of tuberculosis in all cases, and there was no history or other evidence of tuberculosis. The ulcerative lesions of the legs did not occur in nodules and did not have the appearance of tuberculids. In Case 1, in which the ulceration was most extensive, numerous biopsies failed to reveal any evidence of tuberculosis or tuberculids.

Pathology and Physiology.—Microscopic examination of the capillaries in the areas of livedo, as compared with the intervening areas of normally colored skin and areas of skin in parts of the body where livedo was not present, was done in three of our cases, and confirmed the observations of others that visible capillaries in the areas of livedo are considerably more numerous and usually dilated and that the capillary blood flow is slow. It has been stated that the vascular supply of the skin arises as capillary arborizations from arterioles which pierce the cutis from below, and that each of these arborizations anastomoses at its periphery with capillaries from neighboring arborizations. Williams and Goodman[2] have expressed the opinion that the areas of livedo correspond to the peripheral portions of these arborizations, and that the color of the skin near the centers remains normal. Thus, either a spastic or organic obstruction of the arterioles might result in an atonic condition of the capillaries, with marked slowing of the blood flow in the terminal portions of each arborization only, whereas circulation could be adequately maintained and the capillaries remain relatively normal in the central portions of the arborization. The rather small pattern of the livedo in cutis marmorata might be accounted for in this way, but in many cases of persistent livedo reticularis the pattern seems too coarse and the dark areas too large to be explained on such an anatomic basis. Williams and Goodman have expressed the opinion that livedo reticularis is the result of a congenital anomaly of the blood vessels which might show itself early in life as a congenital or childhood disorder, or, later in life, after some disease had affected the arterioles and reduced the arteriolar blood flow.

It had been observed by several of our patients that, after they got into a hot bath, the color of the livid area was at first markedly accentuated, but that, after a time, the color changed from deep purplish-blue to red. This would indicate that the initial increase in blood flow resulted in increased congestion of the atonic capillaries, but that, after a time, the capillary blood flow was increased. Becker noted that, in one of his cases, the injection of epinephrine and pituitrin did not influence the

livedo. In two of our cases a rather marked change was observed after the subcutaneous injection of 10 mg. of mecholyl (acetyl-beta-methylcholine chloride). The usual weakness, tremor, and salivation developed, and, within five minutes, the skin of the lower extremities became definitely pink; this began in the thighs, and progressed slowly to the tarsal regions. As this pink wave spread over the skin the livid areas were completely obliterated, and the patients stated that this was the first time that this had been noted since the onset of the disorder. The effect was not apparent in the distal portions of the feet. Following the pink wave the skin became pale, but the areas of livedo did not reappear for from one to three hours. Typhoid vaccine was administered to four of our patients, and this caused an elevation of systemic temperature and a rise of skin temperature in the toes and legs to 32° C. or more, indicating fairly complete vasodilatation. During these periods the livedo was somewhat less noticeable, but it did not completely disappear.

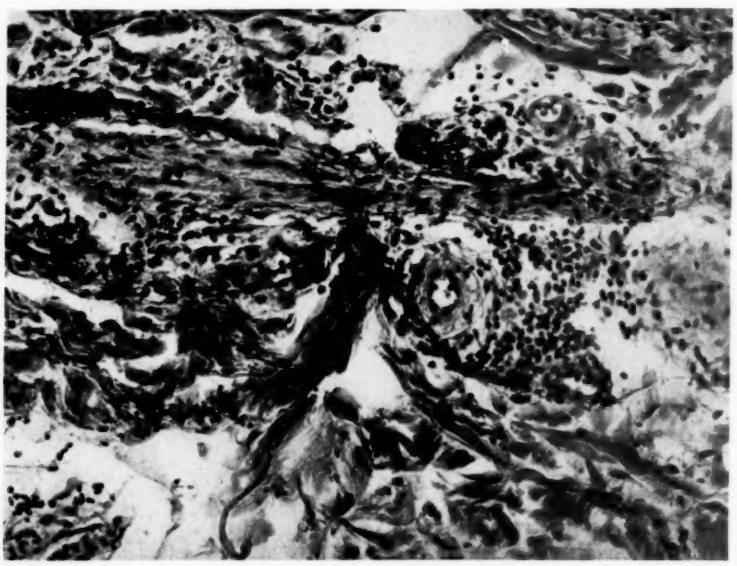

Fig. 4.—Case 6. Biopsy specimen of skin and subcutaneous tissue, showing arterioles with thickened walls and many perivascular lymphocytes (photomicrograph ×175).

Lumbar sympathetic ganglionectomy was followed by a change of the color of the livid areas to pink, except on exposure to extreme cold in one of our cases (Case 1), and by almost complete disappearance of the livedo in the sympathectomized parts in two other cases (Cases 2 and 5). The available evidence would indicate that there is spasm of the arterioles of the skin in the areas where the livedo exists, but that, in addition to this, there is probably some organic change in these arterioles, and that, if this organic lesion becomes extreme, areas of the skin of the legs or of the digits may become gangrenous.

In one of our cases extensive pathologic studies were made and have been reported elsewhere[8]; they indicated that there was definite proliferation of the intima in isolated arterioles and small arteries. Some vessels were completely occluded, and the same lesions were found in a few of the larger veins. In many instances, however, no change was noted in the arterioles of the skin underlying the livid areas, except possibly a slight thickening of the muscular coat. As has been noted, other observers have found proliferation of the intima and also perivascular infiltration and perivascular fibrosis. In two other cases in our series, biopsies of the skin in the livid areas were made. In Case 6, arterioles 75 microns, and less, in diameter, and some of the venules in the cutis were surrounded by collections of lymphocytes (Fig. 4). Their walls were thickened, and their lumina reduced in size. There was no definite proliferation of the intima. The capillaries were numerous and dilated. In Case 13 only a few arterioles were seen, but one of those in the deeper layer of the cutis had a markedly thickened wall and an increase in the number and size of the cell nuclei in the media and adventitia (Fig. 5).

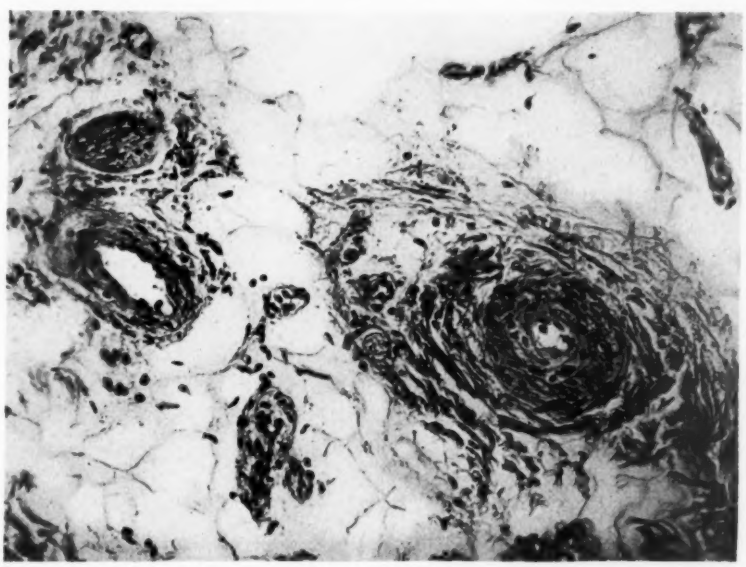

Fig. 5.—Case 13. Biopsy specimen of skin and subcutaneous tissue, showing arteriole with thickened wall, increased number of cell nuclei, and periarterial fibrosis (photomicrograph ×200).

Whether organic or spastic narrowing of the venules and small veins aids in producing the livedo has been a debatable point. Definite inflammatory changes in the veins of the cutis have been noted, but not as consistently as the arterial changes, and it is difficult to prove the existence of spasm of the venules. Conceivably, the capillary dilatation and congestion could be augmented by localized venous obstruction, but probably not produced by it alone. There was incomplete occlusion caused by

intimal proliferation in fairly large veins in Case 1 and this may have been a factor in the development and persistence of the ulcers.

Symptoms.—Persistent livedo reticularis may exist as a benign disorder for many years, with minimal or no discomfort. Most of our patients complained of more or less coldness and occasional numbness of their legs, even at average room temperature, and of accentuation of these symptoms with a decrease in environmental temperature. A few patients stated that there was also rather diffuse pain or aching, particularly in the region of the ankles, during cold weather. However, the only serious symptoms seemed to be in those cases in which ulceration and gangrene occurred. In these cases pain was quite severe and persistent. In Case 1, in which there were peripheral neuritis and extensive recurring ulceration which was refractory to treatment, amputation of both legs was ultimately necessary because of the severe pain and nonhealing of the ulcers.

Diagnosis.—If one regards livedo reticularis as a clinical entity, the diagnosis can be readily made from the appearance of the extremities. The persistence of the discoloration, its blotchy or reticular distribution, and the extent of the involvement (lower extremities to the knees or above, possibly arms and trunk also) distinguish livedo reticularis from Raynaud's phenomenon and acrocyanosis. It can be distinguished from thromboangiitis obliterans by the lack of evidence of occlusion of the larger arteries (normal pulsations), and by the fact that the livid discoloration appears in the legs, which, in our experience, has not been observed in cases of thromboangiitis obliterans. Although definite inflammatory changes in the arterioles have been noted in most of the cases in which biopsies have been made, they are not similar to the changes which occur in thromboangiitis obliterans. In contradistinction, thrombosis or complete occlusion of the lumen is unusual, and the medium-sized and large arteries are not affected. The lesions do not show the medial necrosis which is seen in periarteritis nodosa, and the course of the disease is benign as compared with periarteritis nodosa. Sclerodermatous changes in the skin were not observed in any of our cases, nor have they been described in the literature in association with livedo reticularis.

Treatment.—Since the symptoms are mild in the uncomplicated cases, and the condition may endure for a number of years without evidence of progression, it is doubtful whether any therapy is necessary, other than protection of the body as a whole, and particularly the areas involved, from exposure to cold. Inasmuch as the true cause of the condition is not known, there can be no rational therapy at present. However, patients with livedo reticularis may also have tuberculosis or syphilis, and, if either of these conditions is present, it should receive appropriate treatment. Also, the possibility of poisoning by lead or

arsenic should be considered, and treatment instituted if indicated. In those cases in which there is ulceration or gangrene, a period of rest in bed while these lesions are active and the use of medical and physical vasodilating procedures seem advisable.

As has been stated, lumbar sympathetic ganglionectomy was performed in three of our cases (Cases 1, 2, and 5). In the two cases (Cases 2 and 5) in which there was gangrene of the toes, the livedo reticularis itself almost completely disappeared after sympathectomy; the skin remained warm; symptoms of coldness and aching were relieved, and no further gangrene has developed. The observation period has been three years in Case 2 and one year in Case 5. In Case 1, in which the livedo was intense and widespread and there were extensive, painful ulceration of the legs and arterial occlusion in the toes, lumbar sympathetic ganglionectomy was followed by healing of the ulcers and no recurrence for a year. Also, no further arterial occlusion in the toes developed in this case. However, after that time the ulceration recurred and was progressive, eventually necessitating amputation of both legs. In the sympathectomized parts (below the knees) the livedo was only slightly less prominent, but the discolored areas remained pink rather than blue. In this case a rather severe degree of livedo reticularis of the arms also developed, and a cervicodorsal sympathectomy was done; this had only a slight influence on the livid areas, but relieved the aching and coldness in the hands which accompanied the livedo.

SUMMARY

We have reported a series of thirteen cases of peripheral vascular disease affecting chiefly the legs and feet which seems to us to be best classified under the term "livedo reticularis," as described in the literature. The clinical manifestations differ distinctly from those of Raynaud's disease, acrocyanosis, and thromboangiitis obliterans. These patients did not have evidence of tuberculosis or syphilis, and the circulatory disturbance developed during adult life. The etiology in our cases is not known.

The available data in our cases and others indicate that in livedo reticularis there are usually organic changes in the arterioles of the skin, with chronic vasospasm, which result in regional atony and dilatation of capillaries and slowing of the blood flow. The condition may be complicated by ulceration of the legs and superficial gangrene of the toes. Lumbar sympathetic ganglionectomy resulted in definite improvement in circulation and prevention of further attacks of gangrene in two of our cases and was unsuccessful in one case. It is our opinion that sympathectomy is a justifiable procedure in cases of livedo reticularis in which (1) no definite etiological factor can be found, and (2) superficial gangrene is present.

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DISCUSSION

DR. A. WILBUR DURYEE, New York.—We have seen a number of these cases in and around New York. There is a question I should like to ask Dr. Barker. In taking the history in these cases, did he inquire whether the extremities had been exposed to excessive heat? We find that most of our patients have either stood in front of very hot fires, or have been exposed to excessive sunlight on the beach. You will note that the pictures Dr. Barker showed were mostly of the anterior surfaces of the lower legs and the exposed surfaces of the arms. In most of our cases the lesions were most marked in these localities, and, although it is far from proved, I think that one possible etiological factor is destruction of some of the vessels by excessive heat.

In extensively burned areas one often sees mottling which is very similar to that in the cases which he presented.

I would also like to ask Dr. Barker whether he tried mecholyl iontophoresis as a form of therapy. Many of these patients come to us because of cosmetic faults, and I wonder whether mecholyl iontophoresis had any beneficial effect on the livid appearance.

Two patients whom we have followed have marked hypothyroidism and have responded fairly well to adequate doses of thyroid.

DR. NELSON W. BARKER, Rochester, Minn.—The literature contains descriptions of livedo reticularis which developed after exposure to heat, as was mentioned by Dr. Duryee. None of our patients gave a history of exposure to unusual heat, nor did they work in environments in which this might occur. Also, the livedo was as prominent on the posterior surfaces of the legs and on the soles of the feet as it was on the anterior surfaces of the legs, where exposure to heat might be more likely to occur. We did not treat any of our patients with mecholyl administered by iontophoresis. The injections of mecholyl were used only to obtain information regarding the physiologic disturbance, and not as a therapeutic measure. The suggestion that mecholyl administered by iontophoresis be used in treatment is a good one, although the chronicity of the disease might limit its effectiveness, except during the periods of painful ulceration and gangrene. Livedo reticularis has been described in association with both hypothyroidism and hyperthyroidism. It is doubtful whether there is any etiological relationship between either of these two conditions and livedo reticularis.

OBSERVATIONS ON THE PATHOLOGIC EFFECTS OF THIOCYANATE

An Experimental Study

Howard A. Lindberg, M.D.,* Maurice H. Wald, M.D.,* and
M. Herbert Barker, M.D.
Chicago, Ill.

INTRODUCTION

Aside from any alteration of symptoms or blood pressure of patients with hypertension, the effect of the administration of therapeutic doses of the salts of thiocyanate[1, 2] has consisted chiefly of reduction in the erythrocyte count, hematocrit value, total serum proteins, and plasma cholesterol, and an increase in the erythrocyte sedimentation rate.[3, 21, 22] Not all of these changes occur regularly, but they may be associated with a 1- to 3-month therapeutic blood concentration of 8 to 12 mg. per 100 c.c. Toxic concentrations (15 to 20 mg.) usually bring about or exaggerate these changes.[2] Therefore, toxic doses of the thiocyanate salts were given to dogs for long periods of time in order to extend our knowledge of the pharmacology and toxicology of these drugs.

LITERATURE

No attempt will be made to review the clinical aspects, except to state that the discussion of the "empirical use"[4] of the thiocyanates has continued[1, 5-7] without a good understanding of their pharmacology and toxicology.[1, 2, 5, 8-15 et al.] From the experimental standpoint, reference may be made to the recent review and excellent experimental study of Anderson and Chen.[16]

METHODS

The laboratory procedures which were used include the following: For the determination of blood cholesterol, the method of Bloor[17] was employed; the determination of serum proteins was done by a method adapted from combined techniques of Howe[18], Wu[19], and Koch and McMeekin[20]; a modification of Schreiber's technique[1] for the determination of blood thiocyanate was used. Frequent duplicate analyses by more than one technician were made as a check upon the determination of total proteins and cholesterol.

EXPERIMENTAL OBSERVATIONS ON BLOOD CHOLESTEROL, TOTAL PROTEINS, ERYTHROCYTE COUNT, AND HEMATOCRIT READING

For the purpose of this experiment, twelve normal dogs were given potassium thiocyanate orally in 5-grain (0.3 Gm.) doses. Observation of the blood thiocyanate content at frequent intervals was the guide to

From the Department of Medicine, Northwestern University Medical School, and the Bettie Soper Clements Ward of Passavant Memorial Hospital.
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*Kenneth Smith Fellow in Medicine, Northwestern University Medical School.

daily dosage for the maintenance of toxicosis. The results were tabulated individually for each animal, and the actual values for the blood thiocyanate and the particular constituent being studied are shown side by side.

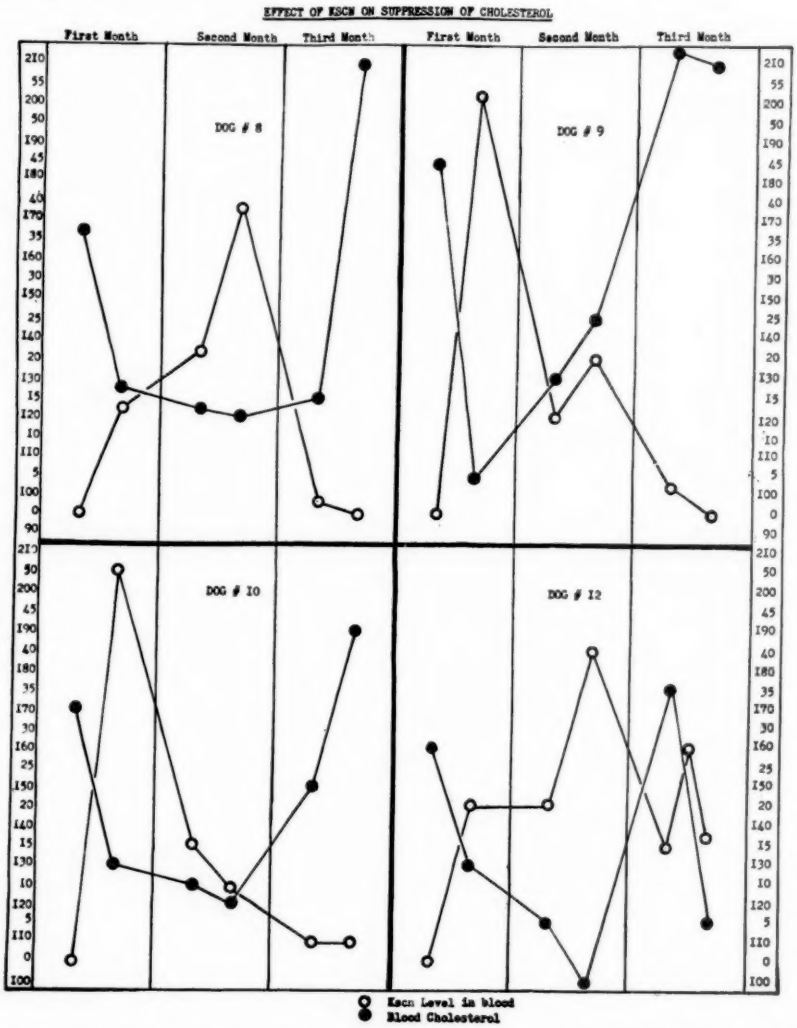

Fig. 1.—Showing the relationship of the levels of blood thiocyanate (mg. %) and plasma cholesterol (mg. %) in Dogs 8, 9, 10, and 12. *KSCN* = potassium thiocyanate (cf. Table I).

For the study of the effect of thiocyanate upon blood cholesterol values (Table I and Fig. 1), a checked duplicate control reading was recorded. It will be noted that in each case a variable but significant fall in blood cholesterol occurred very promptly upon administration of the thiocyanate. It is noteworthy that the fall was abrupt at first, although the actual quantity of thiocyanate in the blood may have been small. In

each case, the subsequent cholesterol level was variable, but a rough parallel between elevation of blood thiocyanate and reduction of blood cholesterol values was apparent. After the original, prompt diminution in cholesterol, the subsequent decline was considerably slower; that is, the gradient of the fall was prolonged over several weeks after a peak in blood thiocyanate value had been reached.

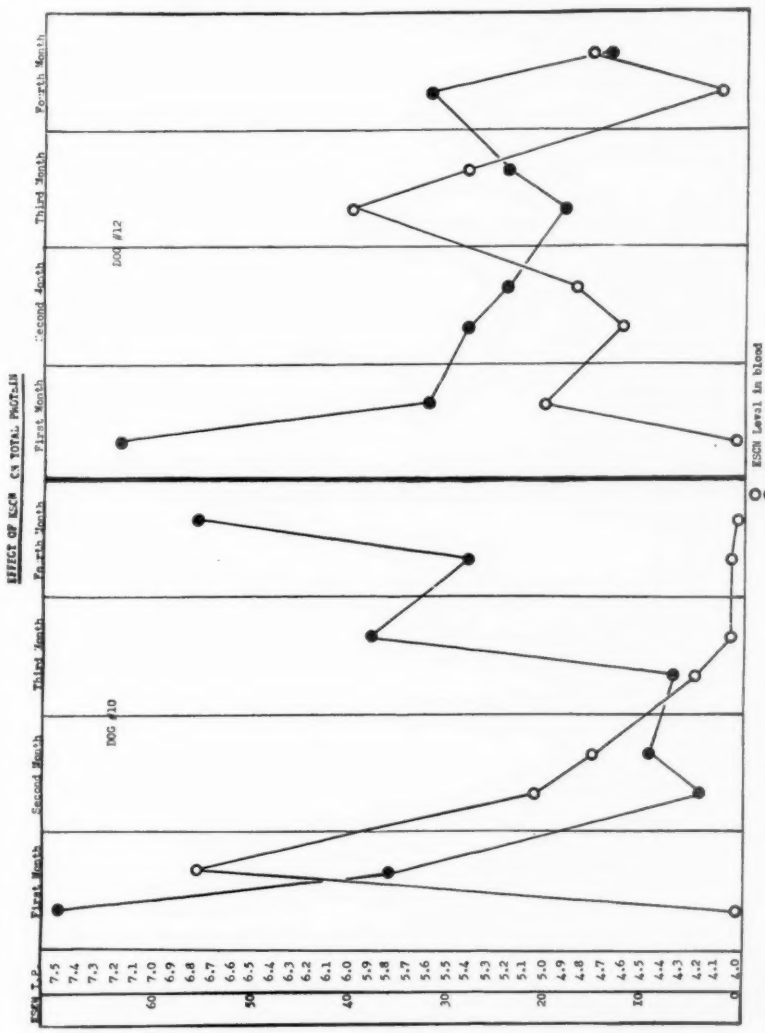

Fig. 2.—Showing the relationshp of the levels of blood thiocyanate (mg. %) and total plasma proteins (%) in Dogs 10 and 12. *KSCN* = potassium thiocyanate (cf. Table II).

There is a tendency for cholesterol values to rise far beyond the original control content when the blood thiocyanate level is permitted to fall (see Table I and Fig. 1).

The response of the blood proteins (Table II and Fig. 2) to thiocyanate is characterized by a prompt initial fall, and by a lag in recovery as the blood thiocyanate level declines. A fall, after a distinct sec-

TABLE

FLUCTUATIONS OF BLOOD CHOLESTEROL (MG. %) IN

DOG	BLOOD	DURATION OF THIOCYANATE											
		0	1	2	3	4	5	6	7	8	9	10	11
4	Sen		5.6			30.3	16		20	13.4	22.2	20.2	14.8
	Chol	172				121			164				232
5	Sen				20	60.2							
	Chol	166				87.5							
8	Sen			3.46		15.7	23	38.4	0	0	0	0	
	Chol	167				126			123	116		125	
9	*Sen*		56	21	0	15.4	20	4.45	0	0	0		
	Chol	194			114		135	147		227	223		
10	Sen					51.5	15.6	8.25	0	0	0		
	Chol	166			131		126	123		149	195		
12	Sen			20	12.4			17	41	16.7	22.2	28.6	
	Chol	160		130				116	89	179		136	
14	Sen					tr	0	17	26 9	3.8	9.5	20.6	
	Chol	150					110	102	80.5	151	186	154	
17	Sen		27.5		0		19.4	27	21.6	10.8	33.4		
	Chol	166	125		142		125	147	167	189	222		
18	Sen		13.9	8.0	75.2		tr	2.36	23			0	
	Chol	169	147	122	117	89	248	250	158	214	348	321	
19	Sen		20	12.2	17.9	37			0				
	Chol	180	87	86.3	93.3	96	143	205	150				

Sen = blood thiocyanate; Chol = plasma cholesterol (cf. Fig. 1.)

TABLE

FLUCTUATIONS OF TOTAL PLASMA PROTEINS (%) IN

DOG	BLOOD	DURATION OF THIOCYANATE											
		0	1	2	3	4	5	6	7	8	9	10	11
4	Sen		5.6			30.3	16		20	13.4	22.2	20.2	14.8
	T. P.	5.5				5.02			5.7		4.89		4.48
5	Sen				20	6.02							
	T. P.	7.0				5.81							
8	Sen			3.46		15.7	23	38.4	0	0	0	0	
	T. P.	7.24		6.13				5.84	6.7	5.84		5.25	
9	Sen		56	21	0	15.4	20	4.45	0	0	0		
	T. P.	7.7		5.8		4.7	4.45	4.36		5.5	5.96	5.4	
10	Sen					5.15	15.6	8.25	0	0	0		
	T. P.	6.6			5.51	4.48	5.8	5.65		5.58	6.6	5.12	
12	Sen			20	12.4			17	41	16.7	22.2	28.6	
	T. P.	7.2		6.0	5.4			5.2	6.5	4.87		5.03	
14	Sen					tr	0	17	26.9	3.8	9.5	20.6	
	T. P.	7.0				5.4	7.8	5.28	5.51	5.48	6.7		
17	Sen		27.5		0		19.4	27	21.6	10.8	33.4		
	T. P.	6.5	6.8		6.5		5.22	4.2		6.5	5.18		
18	Sen		13.9	8.0	75.2		tr	2.36	23			0	
	T. P.	6.9	5.49	5.09	4.29	3.93	5.6	6.9	5.58	6.13	5.65	5.4	
19	Sen		20	12.2	17.9	37			0				
	T. P.	6.5	5.21	5.15	4.3	4.04	6.0	6.45	6.05				

Sen = blood thiocyanate; T. P. = total plasma proteins (cf. Fig. 2).

I

RELATION TO BLOOD CONTENT OF THIOCYANATE (MG. %)

ADMINISTRATION IN WEEKS															
12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
208															
208															
0		15.5													
121		104													
0	15		33.4	28.6	0			3.2	7.6	14.1	14	35		24.4	tr
147	104		138	119	152			158		147	147	166		161	130

II

RELATION TO BLOOD CONTENT OF THIOCYANATE (MG. %)

ADMINISTRATION IN WEEKS													
12	13	14	15	16	17	18	19	20	21	22	23	24	26
5.80	5.58												
7.0													
0		15.5											
5.7		4.73											
0	15		33.4	28.6	0			3.2	7.6	14.1	14	35	24.4
6.7	4.73		5.31		6.22			7.24		6.05	6.35	4.46	5.83

TABLE

DECLINE OF HEMATOCRIT VALUE AND ERYTHROCYTE COUNT

DOG	BLOOD	DURATION OF THIOCYANATE											
		0	1	2	3	4	5	6	7	8	9	10	11
	Scn	0			22.6	9.8	16.6	10.7					
1	Hem	37.6			41	39	39	36	34.8				
	RBC	5.3							3.48				
	Scn	0	13.7										
2	Hem	61	42.5		50	44	22.8						
	RBC	6.3	6.03		4.8								
	Scn		5.6			30.3	16		20	13.4	22.2	20.2	14.8
4	Hem	37	44	41		36.6	24		19.5	20	24		22
	RBC	5.65				5.68	4.37		4.26				4.1
	Scn			3.46		15.7	23	38.4	0	0	0	0	
8	Hem	55	55	39		40	31	35	32	30	32	36	37
	RBC	5.43	5.5			4.25		5.04				4.46	
	Scn		56	21	0	15.4	20	4.45	0	0	0		
9	Hem	47	45	33	39	25	32	11.5		18.1	37		
	RBC	5.95			5.28	2.97					2.27		
	Scn					51.5	15.6	8.25	0	0	0		
10	Hem	46			40	40	37			30	37		
	RBC				5.4	5.4				5.0			
	Scn					tr	0	17	26.9	3.8	9.5	20.6	
14	Hem	51				51							
	RBC	6.3											
	Scn		27.5		0		19.4	27	21.6	10.8	33.4		
17	Hem	51	48		45		45	35	36	30	18		
	RBC	6.3									3.09		
	Scn		13.9	8.0	75.2			0					
18	Hem	54	44		38	27		33					
	RBC	8.14	5.34		5.9		5.5	5.7					
	Scn		20	12.2	17.9	37							
19	Hem	57	53		44		27						
	RBC	8.26		7.35	6.87	5.45	3.97						

Scn = blood thiocyanate; Hem = hematocrit percentage; RBC = Red blood corpuscles in

ondary rise, in total protein value, even though the blood was entirely clear of sulfocyanate, occurred, and no tendency toward a late rise to levels exceeding this original control value was observed. When the blood proteins were diminished, either the albumin or the globulin fraction was more profoundly affected, or both were equally reduced. Clinically, we have observed a diminution of the globulin portion with therapeutic doses of the drug. Experimentally, in these dogs, toxic doses of the drug produced a proportionate reduction of both the albumin and globulin portions.

Turning our attention to the anemia which developed in our animals, we note that Taubman and Heilborn[11] found that fourteen of fifteen guinea pigs which were given two doses of 0.2 Gm. per kilogram of potassium thiocyanate showed a 25 per cent fall in both hemoglobin and erythrocytes. With smaller doses, given orally over longer periods of

III

IN RELATION TO BLOOD THIOCYANATE LEVEL (MG. %)

ADMINISTRATION IN WEEKS															
12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
0 42															
0 39 5.39	15 41		33.4 31 4.62	28.6 31	0 30			3.2	7.6 4.1	14.1	14 30 3.8	35		24.4	

millions (cf. Fig. 3).

time, the hemoglobin and erythrocyte count could be reduced even lower before convulsions ensued.

The fall in the erythrocyte count and the hematocrit value in our series of dogs was striking (Table III and Fig. 3). The gradient in most cases was very gradual. In several instances there was a brief initial rise in the hematocrit value before the fall commenced. The progress of the reduction of the erythrocyte count and hematocrit value was slow and prolonged, persisting at least beyond the limits of these experiments and long after the thiocyanate had been stopped. Following the cessation of administration of the drug there was a slowing of the fall in the erythrocyte count, or an actual arrest of the fall. The hematocrit value, which showed a much wider response, tended to stabilize more quickly after the blood was cleared of thiocyanate. In some animals a slight tendency toward a rise to original levels was indicated.

In attempting to classify this type of anemia, we find that there was a definite fall in hemoglobin, hematocrit reading, and erythrocyte count. The color index and volume index ran somewhat less than 0.8. The Price-Jones curves showed a tendency to shift to the left. The differential leucocyte count was normal. The polymorphonuclear leucocytes and other cells of the granulocytic series were normal despite the intoxication. The reticulocyte count was normal. There was no icterus or hemosiderosis. No change occurred in the fragility of the cells.

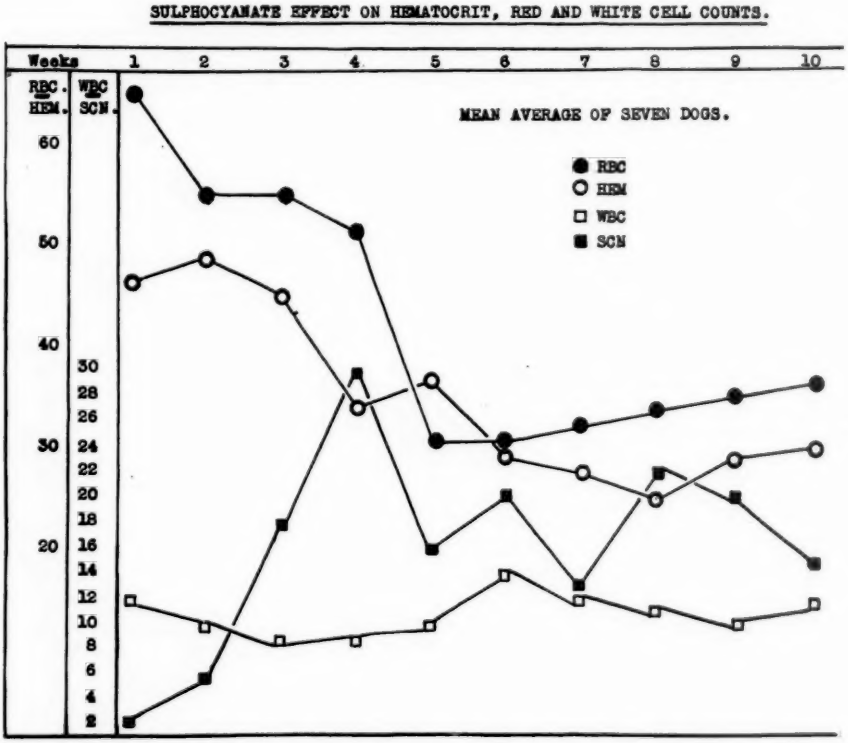

Fig. 3.—Showing the relationship between the hematocrit and erythrocyte levels and the blood thiocyanate curve. The leucocyte level remains essentially unchanged. This graph is a composite of the curves taken from readings on seven dogs, and the curves represent the mean averages. *RBC* = red blood corpuscles in hundred thousands; *HEM* = hematocrit percentage; *WBC* = white blood corpuscles in thousands; *SCN* = blood thiocyanate in milligrams per cent (cf. Table III).

TISSUE STUDIES

It has been shown that thiocyanates permeate all tissues in essentially the same concentration.[2, 13] Hence, the tissue content cannot be presented as evidence favoring one organ or another as the site of their action. Grossly, examination of the bodies of animals and men to whom thiocyanates have been given yields no clues to the action of the drug. However, in our experimental animals, bone marrow sections (biopsy from the sternum, rib, and femur) revealed a relatively acellular bone marrow. In the least severely intoxicated animals, the normal matrix

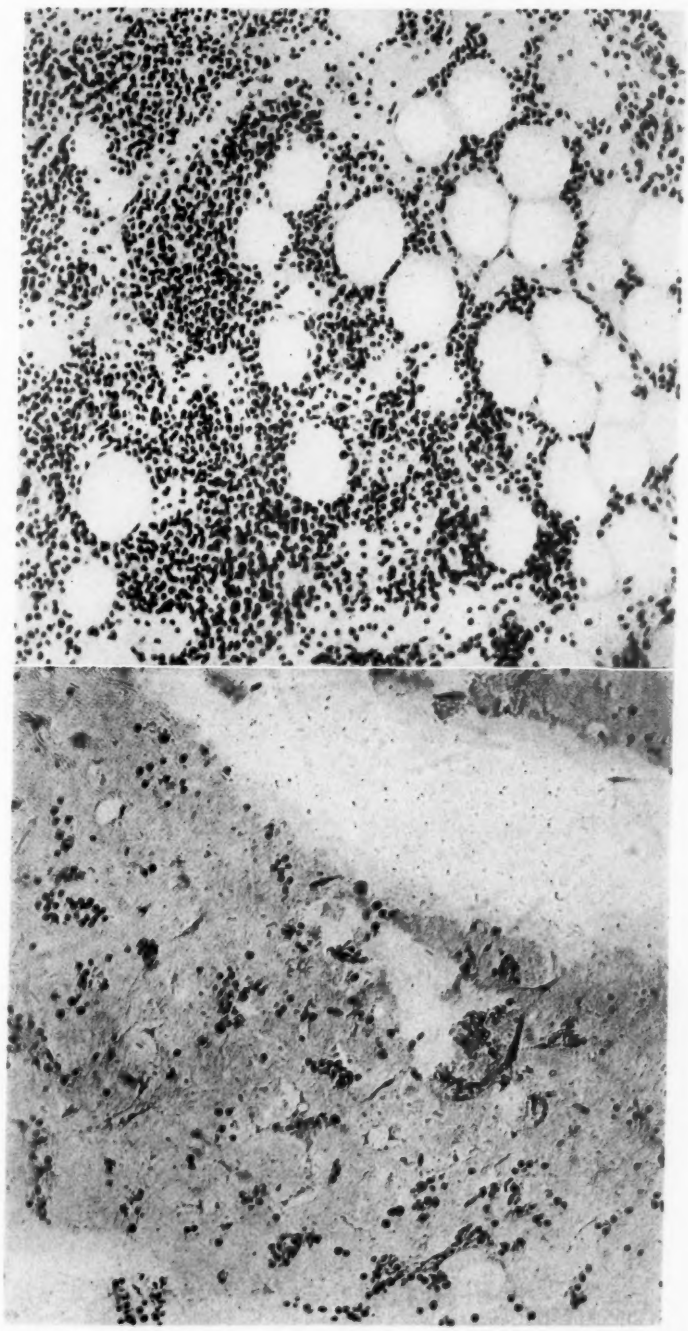

Fig. 4.—Photomicrographs (×250) showing, top, the normal bone marrow of a dog, for comparison with the bone marrow of one of the dogs that had been subjected to prolonged intoxication with thiocyanates. The degeneration in the field shown in the bottom photograph is striking and is wholly typical of the changes observed in the marrow of all of the dogs in the series.

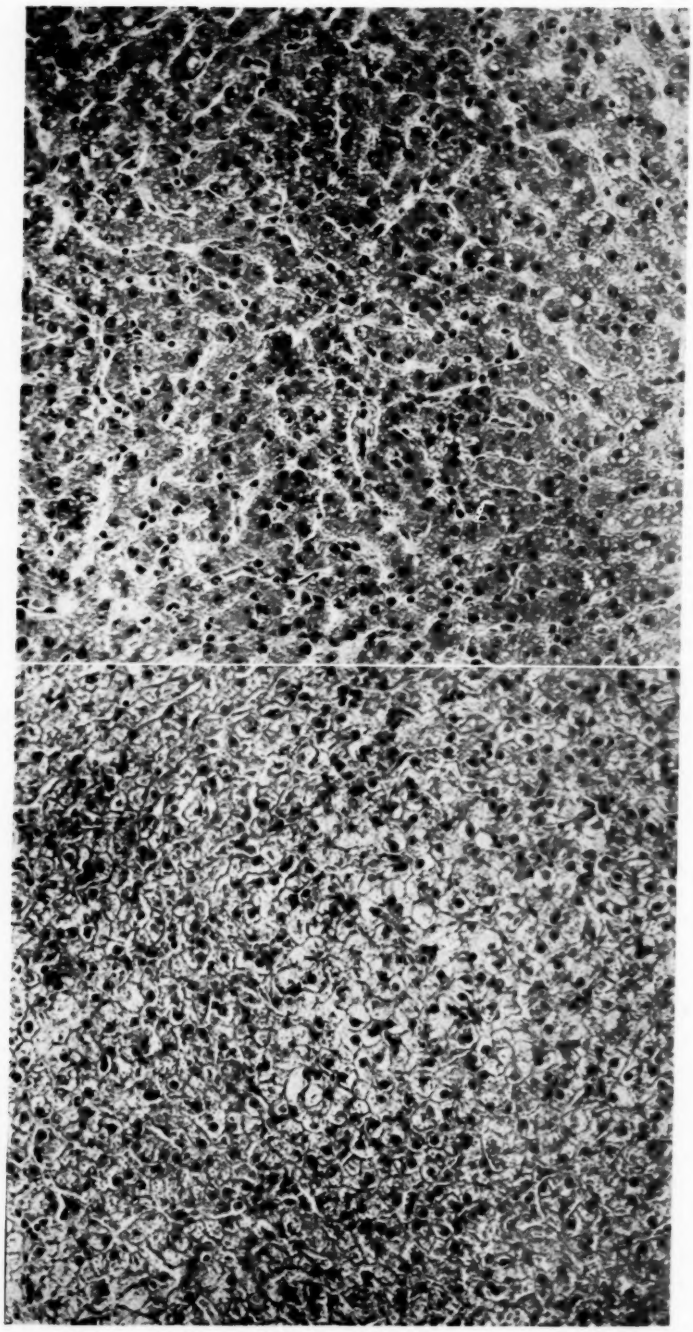

Fig. 5.—Photomicrographs (×250) of the liver of Dog 14. The top photograph shows essentially normal liver tissue which was obtained before the experiment. The bottom photograph shows the degenerative changes which have occurred in the liver of the same dog after prolonged intoxication with thiocyanate. These were observed in all of the dogs of the series.

was replaced by fat. As toxicity became more severe, the fatty marrow was replaced by a clear, light, eosin-staining gelatinous material; the picture was not unlike that of benzol poisoning (see Fig. 4).

Biopsies of the livers were taken before, during, and after the administration of the drug. The livers of dogs which were fed excessive doses of inorganic sulfocyanate salts showed intracellular fatty vacuolization of marked degree (see Fig. 5). The changes were very diffuse, involving the parenchymal cells, and there was practically no tendency toward regeneration or compensatory hyperplasia during the period of study. The icteric index of the animals was never increased. No comparable changes have ever appeared in the tissues of man. However, it may be possible that functional hepatic changes not demonstrable by anatomic methods may occur, as suggested by the alterations in blood cholesterol and total serum protein. Routine examination of the myocardium, kidneys, spleen, pancreas, lungs, and thyroid gland showed no gross or microscopic alteration.

Anatomic changes in the adrenal glands were entirely lacking. Our analyses of human and animal tissue for thiocyanate content did not show that there is a greater quantity stored in this organ than in others. Chemical analyses of the blood, with special reference to sugar metabolism, sodium, potassium, and chloride, also failed to disclose evidence of interference with adrenal function. For these reasons we are unable to support the impression of Healy[12] that "hypoadrenia" may be the principal feature of the toxicology of the thiocyanates.

DISCUSSION

From the standpoint of the work which we have presented here, two points must be made clear. First, many instances of marked lowering of blood pressure in hypertensive patients are observed long before any of these changes in total protein, cholesterol, or formed elements take place. This suggests that a vasodilating effect occurs first, and that the hemic responses, *if they occur at all*, only mirror other systemic alterations. Second, the properly controlled human subjects with hypertension who have been referred to were given only a sufficient quantity of the thiocyanates to maintain blood concentrations that were considered safe (8 to 14 mg. per cent), whereas very toxic amounts (20 to 60 mg. per cent) were given to these normal experimental animals.

CONCLUSIONS

Toxic doses of thiocyanates, when given to normal animals for long periods of time, produced a marked microcytic anemia and a diminution of blood cholesterol and total serum proteins. Tissue studies of these animals showed significant liver and bone marrow changes.

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QUANTITATIVE CHANGES IN THE CAPILLARY-MUSCLE RELATIONSHIP IN HUMAN HEARTS DURING NORMAL GROWTH AND HYPERTROPHY*†

JOSEPH T. ROBERTS, M.D.,‡ AND JOSEPH T. WEARN, M.D., WITH THE TECHNICAL ASSISTANCE OF IRENE BOTEN
CLEVELAND, OHIO

IT IS generally believed that normal growth of the human heart is accompanied by an increase in the diameter and length of the individual muscle fibers, and that when growth is completed, the fibers remain constant in size. In other words, one of the integral parts of growth is an increase in the diameter of the muscle fibers. It is also well known that, as a result of certain pathologic conditions, the heart may undergo hypertrophy, during which the diameter of the cardiac muscle fibers may increase well beyond the limits reached during normal growth. Relatively little is on record, however, of the concomitant changes that occur in the myocardial capillaries during normal growth and hypertrophy of the human heart.

Horvath[2] and Albrecht[3] were among the first to associate cardiac failure with an hypertrophy of the muscle fibers, but the work of Goldenburg,[4] Tangl,[5] Dehio,[6] Stadler,[7] and Letulle[8] established the fact that gross hypertrophy of the heart is the result of enlargement of the individual muscle fibers. Karsner, Saphir, and Todd[9] observed an increase in the fiber diameters in an hypertrophied heart and a decrease in an atrophied heart.

In 1928, Wearn,[10] following Krogh's[11] quantification of capillaries in skeletal muscle, devised a method for counting the capillaries in human and animal hearts. Their counts were high, however, due to shrinkage during fixation of the blocks of muscle. Vannotti,[12] using the method of Wearn, found an initial increase, followed by a decrease, in twelve dogs' hearts during hypertrophy. Petren, Sylven, and co-workers[13-16] and Vannotti[17] have used the benzidene stain of Sjostrand[18] for the counting of myocardial capillaries in guinea pigs and have claimed that during growth, during pregnancy, and following exercise, the capillaries increased in number. The benzidene method stains erythrocytes and not the capillary wall,

From the H. K. Cushing Laboratory of Experimental Medicine in the Department of Medicine of Western Reserve University School of Medicine, and Lakeside Hospital, Cleveland.

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*The experiments reported in this paper have been in progress for several years. Dr. and Mrs. R. A. Shipley and Dr. J. J. Badal took part in some of the earlier experiments. Dr. J. T. Roberts has collaborated during the past four years. (J. T. W.)

†Some of the earlier results of the work were presented before the Society for Experimental Biology and Medicine (1), and before the Association of American Physicians (2).

‡Rees Research Fellow in Medicine.

so, when used for the demonstration of capillaries, it will show only those capillaries which contain erythrocytes at the level at which the capillary is cut. It is extremely rare, in our experience, to find a heart in which the capillaries are evenly filled with red blood cells. Indeed, in sections showing myocardial capillaries cut longitudinally, it is common experience to find long segments of many of the capillaries without a single red cell in them. In sections cut through such areas of the capillaries, the vessel walls would not be shown with the benzidene stain. For this reason, the method in our hands has proved wholly unreliable for the quantification of capillaries.

Shipley, Shipley, and Wearn[19] determined the fiber-capillary ratio, concentration of capillaries, and fiber diameters in fifteen normal and eighteen hypertrophied rabbit hearts. They showed that during growth the myocardial capillaries increased in number to keep pace with the increasing muscle mass. During hypertrophy, however, the fibers increased in diameter, thus causing an increase in the muscle mass, without a corresponding increase in capillaries. As a result of the hypertrophy, therefore, each capillary had a considerably greater mass of muscle to which it supplied blood. Christian[20] has long taught that this change may play a definite role in the failure of the hypertrophied human heart.

MATERIAL

The human hearts used for injection and study in this work were taken consecutively as they came to necropsy, whenever they could be obtained soon enough post mortem to permit successful injection of the capillaries. There was a fairly even distribution as to sex, color, and age in the normal and abnormal groups. Seventy-seven hearts collected over several years' time were used in this study. Eight of these were normal hearts from children of various ages; twenty-six were hearts of normal size from adults, forty were hypertrophied hearts of adults, and three were atrophied hearts of adults who died of wasting diseases.

TECHNICAL PROCEDURES

These hearts were obtained usually within an hour post mortem. After removing the fluid and clotted blood from the chambers, the weight was recorded. Cannulae were tied into the coronary arteries and connected with the injection apparatus. By means of these, the coronary arteries were perfused with oxygenated Locke-Rosenheim solution at a temperature of 37° C. and at a pressure of 80 mm. of mercury. When rhythmical contractions of the chamber were well established, injection of the capillaries was carried out in the manner previously described by Shipley, Shipley, and Wearn.[19] Twelve hearts obtained four to ten hours post mortem were successfully injected by use of the method described by Wearn, Bromer, and Zschiesche,[21] with the exception that 2 per cent Chicago blue in 20 per cent gelatin was substituted for the India ink. The injection pressure used in this latter group was 180 mm. of mercury.

Blocks of tissue were removed for study from each ventricle, and, as nearly as possible, from identical sites in each instance.

In preparing sections of the heart for study, the greatest care was used to prevent shrinkage of the tissue. The method used for imbedding in gelatin and mounting the frozen sections has been described previously.[19] The blocks of fresh tissue

and the mounted sections cut from them were carefully measured to control any shrinkage factor, if present. The freshly mounted sections were counted immediately.

All counts and measurements were made with oil immersion objectives and cross-ruled ocular micrometers, which covered an area of tissue varying, according to the microscope used, from 3,250 to 3,500 square micra. Calibration of these instruments was carried out frequently throughout the study. The capillaries and fibers were counted with the aid of the ruled micrometer ocular in the manner that one counts red blood cells in a ruled counting chamber. Each observer measured in each section all of the first twenty muscle fibers which touched a single point of the ruled ocular micrometer as the slide was moved laterally by means of the mechanical stage. Since many cardiac muscle fibers are elliptical in cross section, both the long and short diameters were measured routinely. These two measurements were averaged separately and then an average of the two was computed for the mean fiber diameter. In making the counts and measurements of capillaries and muscle fibers, microscopic fields with large septa of connective tissue, large arteries and veins, and artificial tears in the section were avoided. Counts and measurements were made only in those fields in which the capillaries and muscle fibers were cut in perfect cross section, and in which the capillaries were completely injected. The identity of the heart on which counts and measurements were being made was unknown to the observer until the observations on that heart were completed. Counts and measurements were made independently on most hearts by three observers, and by at least two observers in all instances.

In addition to the counts of capillaries and the measurements of muscle fibers, the area of connective tissue in each field was estimated by means of the ocular micrometer.

Counts and measurements were made in eight fields of each section by each observer, and the final average was calculated from all observations. The number of observations on each heart was sufficiently large to reduce the probable error of the mean to a point well below the limits dictated by the accepted methods of statistics. Many forms of statistical analysis were tried, but for the sake of brevity, only the arithmetic means, with their probable errors, will be cited.*

NORMAL HEARTS OF CHILDREN

The eight patients in the infants' and children's group ranged in age from slight prematurity to 16 years. All the hearts in this group were normal in every respect, including weight. The ratios of heart weight to body weight were higher than those of the adult group, which is in keeping with the standards generally accepted for children. The heart weights ranged from 13 to 237 Gm., with a mean of 90.8 (±19.0) Gm. The average fiber diameter for the hearts in this group ranged from 6.4 to 11.2 μ, with the mean being 8.96 (±0.38) μ. It is recognized that this is a small group of hearts and that the ages of the children were scattered. There are no hearts from children between the ages of 1 and 8 years. The mean figures for the group, therefore, are not necessarily representative. Table I shows the individual variation.

The concentration of capillaries in the eight children's hearts ranged from 3,230 to 4,513 capillaries per square millimeter, the mean being

*We are indebted to Prof. J. R. Musselman of the Department of Mathematics of Western Reserve University, who reviewed and criticized our mathematical treatment of these data.

3,744 (±122). This average and degree of dispersion showed that the concentration of capillaries in the growing child's heart, regardless of age or of muscle fiber size, remains approximately constant. Thus, the capillary concentration is fairly constant from the time of birth throughout the period of physiologic growth.

TABLE I

NORMAL CHILDREN'S HEARTS

NO.	HEART WEIGHT (GM.)	AGE	HEART WEIGHT-BODY WEIGHT RATIO	FIBER DIAMETER (μ)	CAPILLARIES PER SQ. MM.	FIBER-CAPILLARY RATIO
H85L	13	-3 mo.	0.00655	6.4	3,365	5.90
62	18	3 mo.	0.00927	8.4	4,458	3.81
34	20	3 wk.	0.00690	7.4	4,513	4.04
77	48	10 mo.	0.00768	8.7	3,230	3.30
73	110	8 yr.	0.00478	9.5	3,558	2.10
88	140	11 yr.	0.00400	9.3	4,028	2.04
20	140	11 yr.	0.00353	10.8	3,395	2.39
76	237	16 yr.	0.01096	11.2	3,401	2.25
Average	90.75	5.91 yr.	0.00671	8.96	3,743.5	3.23

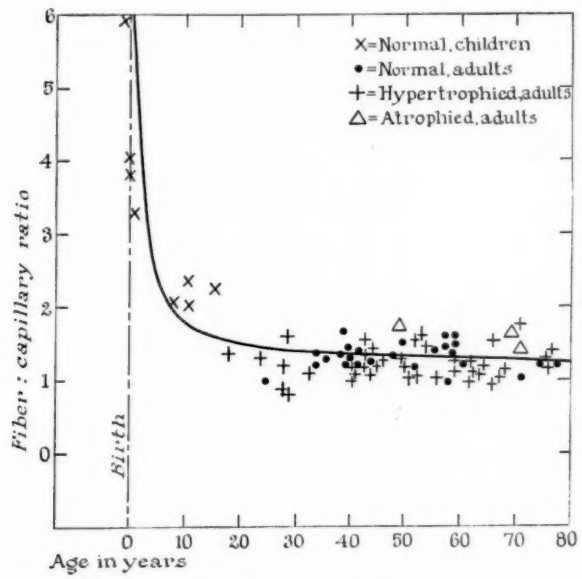

Chart 1.—Changes in the fiber-capillary ratio during growth and hypertrophy.

On the other hand, the ratio of the number of muscle fibers to the number of capillaries per square millimeter—the "FC ratio"*—showed a very significant change during the period of normal growth. From the time of birth the FC ratio was found to decrease during the period of physiologic growth until the ratio approached one (1.34), where it remained throughout normal adult life, as will be

shown later. This decrease in the FC ratio with increasing age occurred in accord with an hyperbolic curve, a type of change frequently encountered in studies of growth phenomena (see Chart 1). Despite the small number of children's hearts, this curve is the same as that found for the growing rabbit hearts.[19] In the heart of a premature infant (three months premature) there were 5.90 muscle fibers to each capillary. The fibers in this heart were very small and the capillary concentration was within normal limits (Fig. 1).

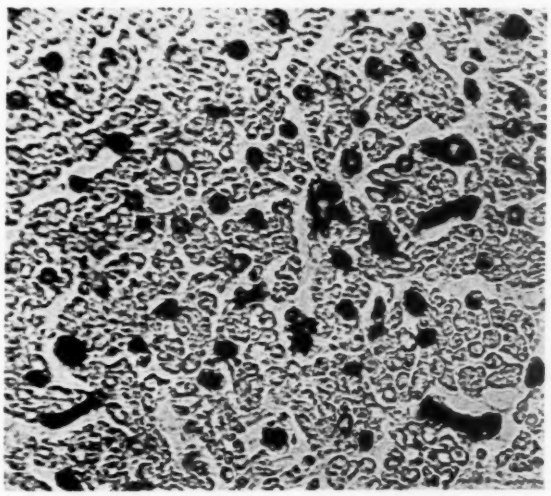

Fig. 1.—Heart weight, 18 Gm. (age 3 weeks). Average fiber diameter, 8.4 μ. Capillaries, 4,458 per square millimeter. FC ratio, 3.81. (This section was fixed and mounted in such a manner as to show the size of the fibers.)

With these observations in hand, it now becomes possible, by deduction, to point out the changes that occur in the myocardial capillaries during physiologic growth of the heart. If the muscle fibers increase in diameter and not in number, and there is a concomitant decrease in the FC ratio, while the capillary concentration remains constant, it is obvious that the capillaries must multiply in order to maintain the capillary concentration at a constant figure as the muscle mass grows. At birth there is approximately one capillary to each four or five muscle fibers, but when adult life is reached, there is approximately one capillary for each muscle fiber. To summarize, therefore, normal growth of the heart is accompanied by a multiplication of the capillaries at such a rate as to maintain a constant concentration of capillaries in the muscle at all times.

NORMAL HEARTS OF ADULTS

In this group of twenty-six patients, death resulted from various diseases, such as pneumonia, meningitis, carcinoma, etc., and some

*The ratio of the number of muscle fibers per square millimeter to the number of capillaries per square millimeter will be referred to hereafter in this paper as the FC ratio.

died following surgical operations. The ages of the patients ranged from 25 to 77 years, the average age being 49.8 (±1.71) years. In the

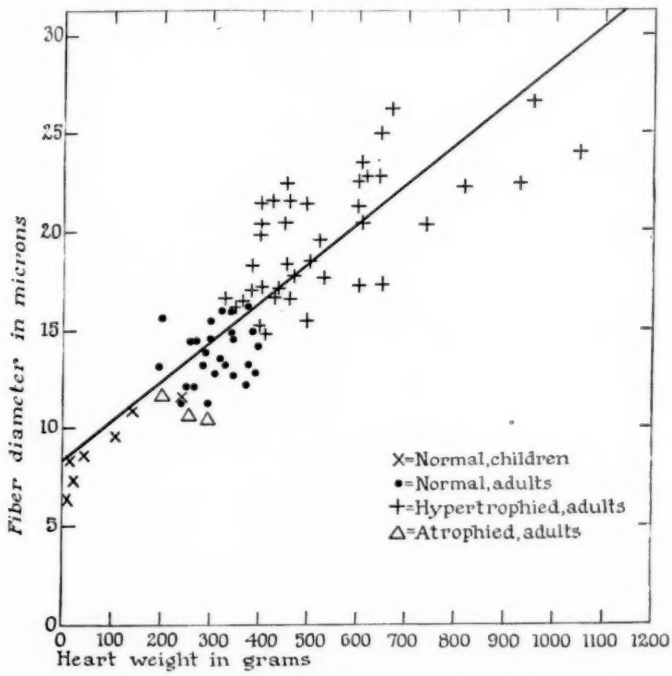

Chart 2.—Relationship of fiber diameter to heart weight during normal growth and hypertrophy of the heart.

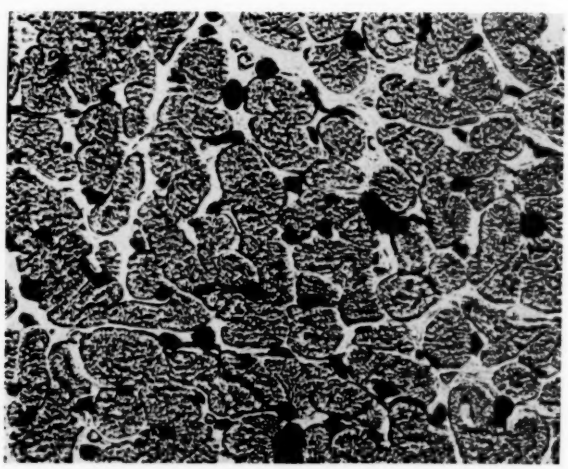

Fig. 2.—Heart weight, 300 Gm. (age 36 years). Average fiber diameter, 15.5 μ. Capillaries, 3,537 per square millimeter. FC ratio, 1.33.

hearts of several of the oldest patients, arteriosclerotic changes were encountered, but so far as could be determined, this finding did not affect the heart weight, fiber measurements, or capillary counts. The

heart weights ranged from 180 to 400 Gm., with an average of 311 (±7.42) Gm. The fiber diameters ranged from 11.5 to 16.1 μ, with a mean for all hearts in this group of 13.9 (±0.2) μ. In Chart 2, which shows the correlation of the heart weights and the fiber diameters, it will be seen that these normal hearts of adults fall into a compact group.

The number of capillaries per square millimeter in this group of hearts ranged from 2,993 to 4,066, the mean being 3,342 (±40). The standard deviation for the entire group is only 8.1 per cent of the mean, which would indicate a fairly uniform concentration of capillaries throughout the group (Fig. 2). When one considers the range in the ages of these patients and the variety of diseases from which they died, and the fact that varying degrees of imperceptible terminal agonal dilatation of the hearts may have occurred, the narrow limits of dispersion of the capillary counts about the mean are of significance.

TABLE II

NORMAL ADULT HEARTS

NO.	HEART WEIGHT (GM.)	AGE (YR.)	HEART WEIGHT-BODY WEIGHT RATIO	FIBER DIAMETER (μ)	CAPILLARIES PER SQ. MM.	FIBER-CAPILLARY RATIO
H29L	180	39	0.00498	13.4	3,114	1.68
39	200	75	0.00740	15.7	3,231	1.29
87	248	59	0.00620	12.2	3,308	1.36
69	262	42	0.00605	14.5	3,405	1.20
83	264	44	0.00427	11.8	3,194	1.26
79	268	52	0.00403	14.4	3,590	1.18
89	275	77	0.00618	12.1	3,414	1.28
45	280	34	0.00400	14.0	4,066	1.36
74	280	58	0.00508	13.2	3,260	1.51
19	290	34	0.00420	11.5	3,390	1.25
46	300	55	0.00380	14.5	3,582	1.46
30	300	36	0.00770	15.5	3,551	1.33
91	304	40	0.00502	13.0	3,030	1.32
58	320	61	0.00689	13.9	3,707	1.05
57	324	25	0.00497	16.0	3,267	0.97
41	326	49		13.6	3,409	1.55
21	336	71	0.00658	14.9	3,092	1.10
47	340	40	0.00790	14.8	3,179	1.46
48	340	40	0.00790	15.9	3,179	1.32
25	342	58	0.00497	13.0	3,368	1.20
72	372	59	0.00490	12.2	3,486	1.36
51	375	59	0.00221	16.1	3,089	1.60
17	375	39	0.00481	13.4	2,995	1.38
84	384	48	0.00548	13.0	2,993	1.36
53	390	58	0.00535	14.3	3,066	1.66
33	400	42	0.00497	15.2	3,939	1.41
Average	310.5	49.8	0.00543	13.9	3,342.5	1.34

There was likewise a remarkable uniformity in this group in the ratio of the number of muscle fibers per square millimeter to the number of capillaries per square millimeter. This FC ratio ranged from

0.97 to 1.68, with an average of 1.34 (±0.03) muscle fibers supplied by each capillary. The remarkable uniformity of this figure throughout this group of normal hearts of adults is in striking contrast to the constantly changing figure found for the hearts of growing children. It seems clear, therefore, that once the growth of the heart is completed, the numerical relationship of the fibers and capillaries becomes and remains constant, so long as the heart muscle remains normal.

Several of the adult hearts might well have been placed in either the normal or hypertrophied group. Their classification was decided upon after careful study of the history, autopsy findings, heart weight-body weight ratio, and fiber diameter in each instance. The weights of these hearts were in the region of 400 Gm., and they account for the overlapping of the fiber diameters and the capillary counts in the normal and hypertrophied groups. Exchanging the grouping of any of these doubtfully classified hearts, however, would not affect significantly any of the statistical conclusions derived.

The inclusion of one heart (No. 30) in the group of normal hearts also calls for an explanation. The valves were the seat of mild chronic rheumatic valvulitis and subacute bacterial endocarditis, but there was no hypertrophy, and the heart weight-body weight ratio, muscle fiber measurements, and capillary counts fell within the normal range.

HYPERTROPHIED HEARTS OF ADULTS

In the group of patients with hypertrophied hearts there was, in every instance, both clinical and pathologic evidence of heart disease. Hypertension, rheumatic fever, syphilis, and arteriosclerosis of the coronary vessels were the most common causes of the cardiac hypertrophy. In the majority of these patients death resulted from congestive heart failure. In a few of the hearts the weights were such that they might well have been placed in the borderline group described above, but the presence of heart disease and of definite, though slight, hypertrophy seems sufficient reason for placing them in this class.

The age distribution in this group was almost identical with that of the normal adult group, the range being from 18 to 77 years, with a mean of 51.0 (±1.55) years. The mean for the normal adult group was 49.8 years.

The weight of the hearts ranged from 326 to 1,050, with a mean of 538 (±18) Gm. The average muscle fiber diameters ranged from 14.8 to 26.5 μ, with a mean of 19.9 (±0.30) μ. As will be seen in Chart 2, there is a direct proportion between the heart weight and the muscle fiber diameter in these hypertrophied hearts. It is obvious, of course, that both of these figures fall well above the ranges for the heart weights and muscle fiber diameters in the group of normal hearts.

The finding of greatest interest and importance was the definite decrease in the concentration of capillaries in the hypertrophied hearts.

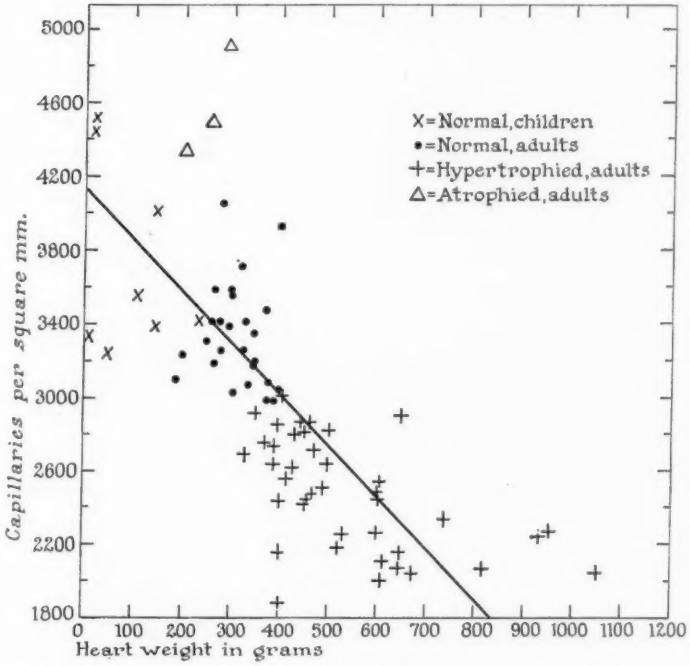

Chart 3.—Concentration of capillaries in normal, hypertrophied, and atrophied hearts.

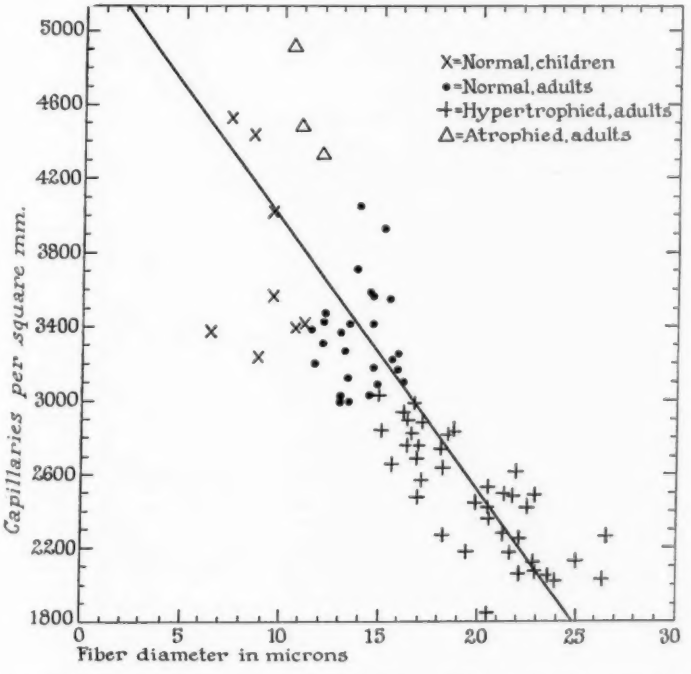

Chart 4.—Relationship of the concentration of capillaries to fiber diameter in normal, hypertrophied, and atrophied hearts.

The capillary concentration ranged from 1,868 to 3,037 per square millimeter, with a mean of 2,483 (±31). A comparison of these figures with those of the normal hearts of adults and children (Charts 3 and 4) shows that the trend of the figures for the capillary concentration of hypertrophied hearts is conspicuously lower than those of the normal hearts. The decrease in capillary concentration was clearly due to the increase in diameter of the muscle fibers which, as they enlarged, pushed the capillaries farther apart (Figs. 3 and 4). Moreover, the concentration of capillaries diminished in proportion to the increase in fiber diameter and heart weight.

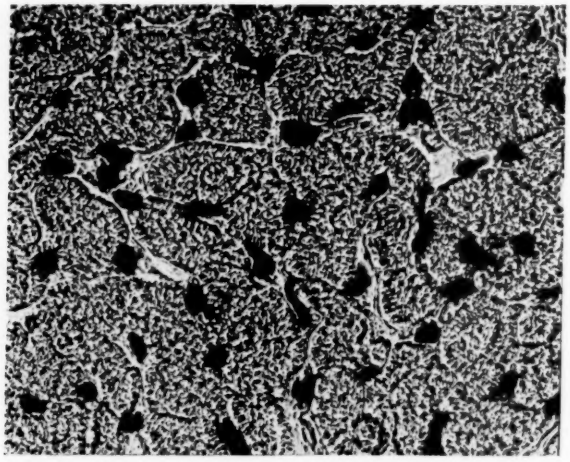

Fig. 3.—Heart weight, 600 Gm. (age 63 years). Average fiber diameter, 22.8 μ. Capillaries, 2,485 per square millimeter. FC ratio, 1.13.

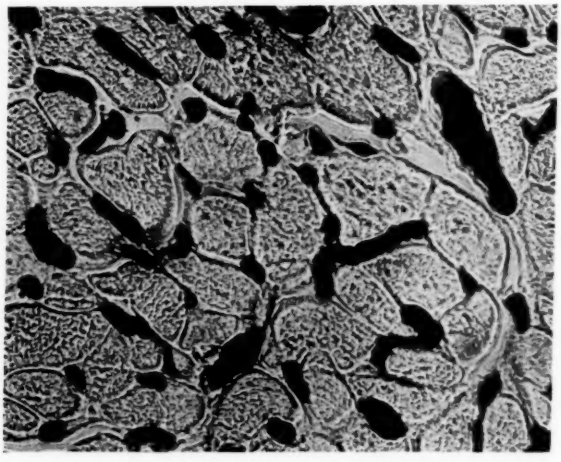

Fig. 4.—Heart weight, 960 Gm. (age 33 years). Average fiber diameter, 26.5 μ. Capillaries, 2,270 per square millimeter. FC ratio, 1.08.

The remarkable uniformity of the fiber-capillary ratio observed in the normal hearts of adults also held true in the hypertrophied hearts.

TABLE III

HYPERTROPHIED ADULT HEARTS

NO.	HEART WEIGHT (GM.)	AGE (YR.)	HEART WEIGHT-BODY WEIGHT RATIO	FIBER DIAMETER (μ)	CAPILLARIES PER SQ. MM.	FIBER-CAPILLARY RATIO
H70L	326	43	0.00465	16.7	2,694	1.50
43	350	53	0.00745	16.1	2,922	1.65
80	370	64	0.00587	16.3	2,748	1.13
56	380	44	0.00595	18.2	2,640	1.44
61	380	18	0.00792	17.0	2,745	1.38
44	390	52	0.00557	15.1	2,847	1.58
15	400	51	0.00743	19.8	2,438	1.05
16	400	39		21.7	2,173	0.97
13	400	41	0.00687	20.5	1,868	1.57
32	409	66	0.00902	14.8	3,037	1.57
81	415	68	0.00486	17.2	2,558	1.16
14	425	59	0.00810	21.9	2,612	1.12
68	430	46	0.00796	16.7	2,821	1.26
92	439	77	0.00655	17.2	2,874	1.42
65	450	64	0.00958	18.5	2,819	1.16
18	450	44	0.00500	20.5	2,413	1.10
66	455	41	0.00723	22.5	2,430	1.08
71	460	54	0.00523	16.4	2,892	1.49
60	464	67	0.00930	21.8	2,470	1.04
54	470	28	0.00795	18.0	2,727	1.21
42	487	62	0.00715	21.4	2,494	1.26
94	493	24	0.00778	15.7	2,647	1.37
28	500	59	0.00910	18.7	2,835	1.29
78	521	50	0.01023	19.4	2,186	1.18
90	529	29	0.00762	18.1	2,260	1.35
26	600	71	0.00925	17.2	2,488	1.36
27	600	49	0.00822	21.2	2,264	1.28
40	600	63	0.00790	22.8	2,477	1.13
67	604	56	0.01109	20.6	2,526	1.05
86	608	41	0.01030	23.6	2,063	1.02
82	614	66	0.00627	22.9	2,115	0.99
63	645	45	0.00965	22.9	2,082	1.20
75	647	52	0.00880	25.0	2,139	1.05
37	650	76	0.01140	16.9	2,959	1.22
59	670	62	0.01265	26.3	2,040	1.02
93	735	43	0.01234	20.3	2,352	1.22
55	820	70	0.01200	22.1	2,077	1.30
52	930	43	0.01691	22.1	2,257	1.36
38	960	33	0.01433	26.5	2,270	1.08
97	1050	27	0.01690	23.8	2,073	0.89
Average	538.2	51	0.00878	19.86	2,483.4	1.24

The average number of fibers supplied by each capillary was 1.24 ($\pm$0.020), with a range of 0.89 to 1.65. Thus, the average FC ratio of hypertrophied hearts is remarkably close to that of the normal hearts of adults (1.34). Whether this slight difference is of any significance statistically, we are not prepared to say. From a practical viewpoint, however, the evidence seems convincing that the capillaries do not multiply during hypertrophy to keep pace with the increase in the muscle mass, as they do during normal growth of the heart. With the decrease in capillary concentration in an hypertrophied heart,

each capillary is called upon to supply a larger mass of muscle, and this mass increases proportionately with the weight of the heart.

ATROPHIED HEARTS OF ADULTS

There were three hearts which showed atrophy of the muscle. Death in these instances resulted from carcinoma, cerebral hemorrhage, and peritonitis, and at the time of death, marked generalized emaciation was noted. In two of the hearts a moderate amount of arteriosclerosis was present, but otherwise no abnormalities were found. The capillary concentration, fiber size, etc., are shown in Table IV.

TABLE IV

ATROPHIED ADULT HEARTS

CASE	HEART WEIGHT (GM.)	AGE (YR.)	HEART WEIGHT-BODY WEIGHT RATIO	AVERAGE FIBER DIAMETER	CAPILLARIES PER SQ. MM.	FIBER-CAPILLARY RATIO
H31L	200	71	0.00294	11.9	4,379	1.48
35	257	70	0.00505	10.9	4,515	1.76
36	285	49	0.00500	10.5	4,946	1.83
Average	247.3	63.3	0.00433	11.1	4,613.3	1.69

TABLE V

CHANGES IN THE CAPILLARIES AND FIBERS

	HEARTS OF CHILDREN	HEARTS OF ADULTS		
		NORMAL	HYPERTROPHIED	ATROPHIED
Number of cases	8	26	40	3
Heart weight (Gm.)	90.8 (±19.0)	310.5 (±7.42)	538 (±18)	247.3
Age (years)	5.91 (±1.52)	49.8 (±1.7)	51.0 (±1.55)	63.3
Fiber diameter (μ)	8.96 (±0.38)	13.9 (±0.2)	19.86 (±0.30)	11.1
Capillaries/sq. mm.	3744 (±122)	3342 (±40)	2483 (±31)	4613
Fibers per capillary	3.23 (±0.32)	1.34 (±0.03)	1.24 (±0.02)	1.69

This group is too small to justify any conclusions, but in all three cases where there was cardiac atrophy, the average size of the muscle fibers was smaller than normal and the concentration of capillaries was increased above the normal figure. The obvious interpretation is that, with the decrease in size of the muscle fibers, the capillaries lie closer together. In these three instances the FC ratios were abnormally high, but our observations do not furnish any explanation for these findings.

DISCUSSION

When one studies the data presented in this report bearing upon the quantitative relationship of the capillaries to the heart muscle mass, it becomes obvious that a high order of correlation exists; so high, indeed, that it strongly suggests an underlying biologic law

which may govern these processes. Between the average fiber diameter and the number of capillaries per square millimeter, for instance, there is a very close correlation. This takes the form of a high negative rectilinear correlation, the coefficient of which is "minus 0.839 (±0.023)." From the regression lines, the capillary concentration in the heart can be calculated from the known average fiber diameter by the following formula:

Capillaries per square millimeter = 3947 − (119.95 × fiber diameter)

The probable error for the predicted value is ±226 capillaries per square millimeter. For the most part, the figures for our individual hearts, as shown in Chart 4, show very little deviation from the plotted straight line of closest fit.

There is also a high positive (i.e., direct) rectilinear correlation between the heart weight and the average muscle fiber diameter. The correlation coefficient, with its probable error, for these two is "plus 0.872 (±0.019)." If the heart weight is known, the average muscle fiber diameter can be calculated by the formula:

$$\text{Fiber diameter} = 8.22 + (0.0199 \times \text{heart weight})$$

The probable error for the predicted value is only ±1.51 μ. This correlation is rectilinear, and, as will be seen in Chart 2, all of our individual observations fall very close to the plotted straight line of closest fit.

Since these two correlations exist, a very close correlation between the actual heart weight and the capillary concentration would naturally be expected. This proved to be a high degree of negative rectilinear correlation, with a correlation coefficient and its probable error of "minus 0.745 (±0.035)." The capillary concentration per unit of area can be calculated from the actual heart weight by the formula:

Capillaries per square millimeter = 3,975 − (2.425 × heart weight)

The probable error for the predicted value is ±295 capillaries per square millimeter. For the most part our cases show little dispersion from the plotted straight line of closest fit. The explanation of the dispersion of the few that deviate more widely is clear when the fiber size and the clinical and pathologic conditions are considered.

From our data, the correlation between the age of the subject and the FC ratio also appears to be a close one. In this instance the correlation is a negative one and is curvilinear, the curved line of closest fit for our data resembling an hyperbolic type of curve similar to those frequently encountered in studies of growth phenomena (see Chart 1). The correlation ratio, with its probable error for age (X) and the FC ratio (Y), is expressed by the formula:

$$\text{Eta}_{YX} = 0.914\ (\pm 0.015)$$

The FC ratio may be predicted from the patient's known age by the formula:

$$\text{FC ratio} = \frac{5.67}{\text{Age} - 0.14} + 1.20$$

The portion of the curve on the right side of Chart 1, i.e., the part dealing with the adult hearts, is practically a horizontal straight line. The curve indicates very clearly the two types of vascular change during enlargement of the heart. The first is the multiplication of capillaries, which maintains a constant capillary concentration during the physiologic growth period of the heart, and the second is the actual decrease in the capillary concentration which occurs when the heart hypertrophies as a result of disease. These results, although based upon results in a small number of children's hearts, are in agreement with those of Shipley, Shipley and Wearn.[19]

The amount of connective tissue lying between the muscle fibers and the capillaries in the large muscle planes did not vary significantly in the normal and hypertrophied hearts. This tissue was estimated by means of the ocular micrometer. The average percentage of interstitial connective tissue in the hearts of the children was 3.15; in the normal hearts of adults, 4.54; and in the hypertrophied hearts, 4.61. It should be pointed out that the method of measurement did not include observations on the large connective tissue septal sheaths lying between the muscle planes.

Our method of counting capillaries and measuring muscle fibers called for an even distribution of muscle fibers and a complete injection of the capillary bed. These requirements eliminated those areas in the sections which contained large fibrous and necrotic scars resulting from arteriosclerosis or rheumatic fever. We have purposely confined this report to the observations on the unscarred normal and hypertrophied muscle. (The effect of arteriosclerosis, hypertension, syphilis, and rheumatic fever upon the capillary-fiber relationship, etc., will be reported upon in a separate communication.)

A comparison of the areas of the average muscle fibers is of interest in that it emphasizes the differences between the normal and hypertrophied hearts of the adult group. The average fiber area, based on the formula for the area of an ellipse, was calculated from the measurements of the diameters of the cross section of the individual muscle fibers. The average area of a fiber for the hearts of children of various ages was 63.3 sq. μ; for the hearts of normal adults, 148.4 sq. μ; and for the hypertrophied hearts, 306.5 sq. μ.

The average area of tissue supplied by each capillary was found to be 267 sq. μ for the hearts of children; 299 sq. μ for the normal hearts of adults; and 403 sq. μ for the hypertrophied hearts. Thus, the area supplied by each capillary was essentially the same in the hearts of

children and normal adults, but considerably greater in the hypertrophied hearts.

The capillary surface area may be obtained approximately by the formula for the surface of a cylinder 1 cm. in length with a diameter equal to that of the capillary; this, multiplied by the number of capillaries per square centimeter, gives the surface area of the capillaries in 1 c.c. of heart tissue. The diameter of the capillary was assumed in this calculation to be that of a red blood corpuscle in each group of hearts. By this method the capillary surface area per cubic centimeter of tissue was found to be 882 sq. cm. for the children's hearts, 787 sq. cm. for the normal hearts of adults, and 585 sq. cm. for the hypertrophied hearts.

When the muscle fiber volume in 1 c.c. of heart tissue was calculated from the average area of individual fibers and the number of fibers per square centimeter of heart tissue, using the formula for the volume of a cylinder, the percentage of muscle fiber in 1 c.c. of heart tissue was 77 per cent for the children's hearts, 67 per cent for normal hearts of adults, and 94 per cent for hypertrophied hearts.

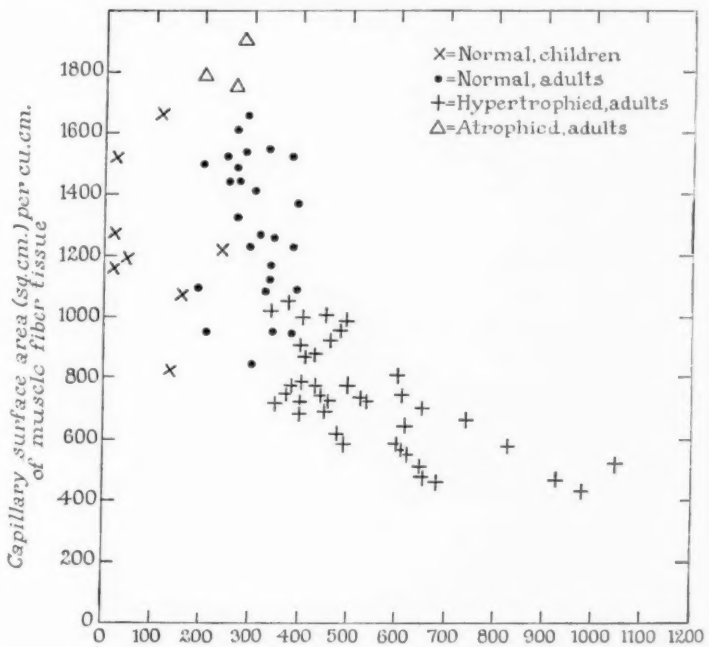

Chart 5.—Capillary surface area in normal, hypertrophied, and atrophied hearts.

The ratio of the capillary surface area to the percentage of muscle tissue per cubic centimeter of heart tissue gives an approximation of the capillary surface area available for diffusion of oxygen and metabolites to and from 1 c.c. of contractile muscle fiber substance. This was

found to be 1,145 sq. cm. for children's hearts, 1,184 sq. cm. for normal hearts of adults, and only 625 sq. cm. for hypertrophied hearts. When this ratio is plotted against heart weight in the individual cases (Chart 5), the normal hearts of children and adults are spread over a wide range, without any apparent correlation with heart weight. The hypertrophied hearts, however, fall into a range well below the normal ones and seem to show a definite rectilinear negative correlation of high degree with heart weight. The wide range of the normal hearts is in keeping with the great capillary reserve recognized in other organs such as the kidney, skeletal muscle, lung, etc. In other words, it suggests a wide margin of safety for the heart.

It is obvious, of course, that these mathematical applications only bring out more clearly the points established by the anatomic data. They show quite clearly that during normal growth the capillaries of the heart multiply to keep pace with the growing muscle fibers, while during hypertrophy, on the other hand, the muscle fibers enlarge, without increase in the number of capillaries, and as a consequence, the capillaries are pushed farther apart. As a result, each capillary has to supply an increasing mass of muscle as the heart hypertrophies. This means that the distance from the capillary wall to the periphery of the muscle mass which it supplies increases as the heart hypertrophies, thus lengthening the route over which the metabolic products have to travel and increasing the amount of tissue through which oxygen has to diffuse in proportion to the degree of hypertrophy.

If one accepts the calculations of Hill,[22] indicating that oxygen diffuses through a thick muscle fiber with greater difficulty than through a thin one, and if Krogh's formula[11] for the oxygen diffusion index is applicable, it is highly probable that at some stage of cardiac hypertrophy a point is reached where the distance between the capillary and the periphery of the muscle mass which it supplies becomes so great that the exchange of oxygen and metabolites between them is impeded. It is not the purpose of this paper either to support or to deny this thesis, but experiments which it is hoped may throw light on this question are now in progress in our laboratory.

CONCLUSIONS

In the human heart at birth the ratio of muscle fibers to capillaries is approximately 6:1.

During the process of growth the fibers increase in size and the capillaries multiply. At maturity the muscle fiber-capillary ratio becomes approximately 1:1, where it remains throughout adult life.

The concentration of capillaries per square millimeter of muscle tissue is constant from birth throughout normal life.

During hypertrophy the muscle fibers enlarge, the capillaries do not multiply, and as a result, an actual decrease in concentration of capillaries results.

In three atrophied hearts the muscle fibers showed a decrease in size, with a resulting increase in capillary concentration.

We wish to express to Prof. Howard T. Karsner and his staff in the Institute of Pathology our deep appreciation of their cooperation in obtaining material for this study and of their interest and helpful criticisms throughout the work.

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THE "ANOXEMIA TEST" IN THE DIAGNOSIS OF CORONARY INSUFFICIENCY

ROBERT L. LEVY, M.D., NORMAN E. WILLIAMS, M.D.,
HOWARD G. BRUENN, M.D., AND HENRY A. CARR, M.D.
NEW YORK, N. Y.

IN A previous communication,[1] it was proposed that changes in the form of the electrocardiogram caused by induced generalized anoxemia might be used as an index of the functional efficiency of the coronary circulation. A simple apparatus suitable for producing oxygen want had already been described.[2] Tentative criteria for an abnormal response were established. Other uses to which the method might be put were suggested. It has already been applied to the study of the effect of various drugs on the coronary arteries in patients with anginal pain and has served to demonstrate the value of certain of these as coronary dilators.[3, 4] In the present paper, further experiences with the "anoxemia test" are related; the criteria for an abnormal response are modified; reactions to induced oxygen want are described; and the limitations, as well as the clinical applications of the test, are discussed.

TECHNIQUE

For convenience, the apparatus and procedure are again described. The only difference in the apparatus as it is now used is the addition of a humidifier. This has eliminated the dryness of the throat of which a number of patients previously complained. The manner of carrying out the test is unchanged.

Apparatus (Figs. 1 and 2).*—A tank containing a mixture of 10 per cent oxygen and 90 per cent nitrogen furnished an unvarying concentration of oxygen in the inspired air.† The oxygen mixture was admitted at a rate comparable to that of normal pulmonary ventilation. The gas was allowed to flow, through a humidifier, into a rubber bag, which was kept full, but not distended. Two flutter valves were incorporated in such a way that the mixture was inhaled during inspiration and exhaled during expiration, without rebreathing. A two-way valve at the mouthpiece enabled the observer to connect the patient to the apparatus while he was breathing room air, and thus accurately to record the time at which the subject began breathing the low-oxygen mixture. A tank containing 100 per cent oxygen was also in the circuit, so that, if desired, by turning a needle valve, anoxemia could be relieved quickly.

Procedure.—Observations were made at least two hours after the last meal. The temperature of the room in which the test was made was kept reasonably constant

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From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Medical Clinic of the Presbyterian Hospital.

*The apparatus may be obtained from the Foregger Co., 55 W. 42nd St., New York City.

†The tanks of 10 per cent oxygen were obtained from the Ohio Chemical Co. The composition of the mixture was checked at frequent intervals, and was found to vary not more than ± 0.6 per cent.

at about 72° F.* The subject was allowed to rest quietly in bed for a period varying from thirty minutes to an hour. The procedure was explained, and he was told that if he experienced pain in the chest or arms he should at once raise his hand. The

Fig. 1.—Apparatus ready for use.

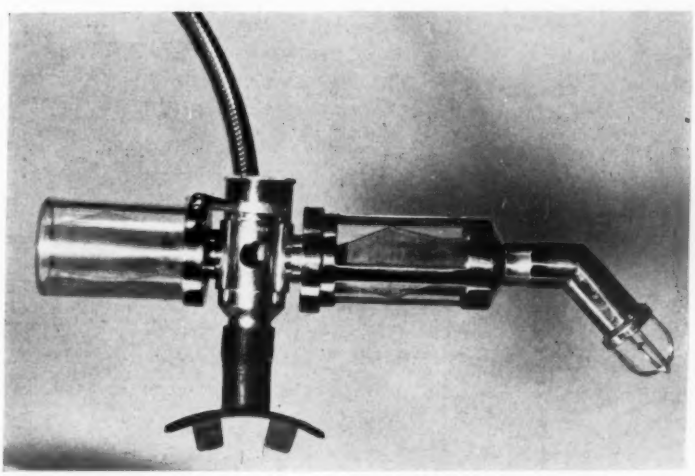

Fig. 2.—Mouthpiece, control valve, flutter valves, and connection for bag.

electrodes were applied and remained in place throughout the test. The mouthpiece of the gas apparatus was then inserted, and a nose clamp adjusted. The subject was

*In patients who are subject to anginal attacks, exercise tolerance is reduced shortly after taking food, but is unaffected by variations in the external temperature (Wayne, E. J., and Graybiel, A.: Observations on the Effect of Food, Gastric Distension, External Temperature, and Repeated Exercise on Angina of Effort, with a Note on Angina Sine Dolore, Clin. Science **1**: 287, 1933-1934). Using our method for inducing anoxemia, it has been shown recently that anginal pain appears earlier when the test is done on a patient with a full stomach than during the fasting state (Gilbert, N. C., Fenn, G. K., and Le Roy, G. V.: The Effect of Distention of Abdominal Viscera on the Coronary Blood Flow and on Angina Pectoris, J. A. M. A. **115**: 1962, 1940.

allowed to breathe room air through the valve of the apparatus for a few minutes. At this time a four-lead electrocardiogram was taken as a control. The precordial lead was the one commonly designated as IVF. The test was then started by closing the valve; the subject was unaware of this maneuver. The standard period of inhalation of the 10 per cent oxygen mixture was 20 minutes, for it was found that within this time electrocardiographic changes usually appeared in cases of coronary sclerosis; when the anoxemia was continued longer, the subjects tended to become restless and uncomfortable. Additional electrocardiograms were taken at the end of 5, 10, 15, and 20 minutes. If pain was experienced, or if there were signs of an undesirable reaction at any time during the test, an electrocardiogram was taken at once, the low-oxygen mixture was shut off, and 100 per cent oxygen was administered for approximately one minute. Electrocardiograms were again taken 1, 5, and 10 minutes after the latter procedure, with the mouthpiece still in place and with the patient breathing room air through the control valve.

For ordinary clinical purposes it suffices to take only three records, namely, a control; a second at the end of twenty minutes (or upon the appearance of pain or other discomfort); and a third, five minutes after 100 per cent oxygen has been given for one minute. The last record serves to demonstrate that such changes as may have taken place can be partly or wholly abolished when anoxemia is relieved.

In each lead measurements were made of the deviation of the RS-T junction and the amplitude of the T wave. The direction of the T wave was also indicated. The heart rate was counted in Lead II. Measurement of the P-R and QRS intervals was omitted because it had been previously shown that these did not vary significantly.[1] The data from each test were charted on individual sheets.

Deviation of the RS-T junction, measured in millimeters, was taken as the difference in level between the point just preceding the initial deflection of QRS and the point immediately following its final deflection. In measuring a given record, either the upper or the lower margin of the string shadow was used in establishing both points. Care was taken to select complexes which ran horizontally. All of the records were read independently by at least two observers. A Cambridge string-galvanometer electrocardiograph was employed. Standardization of the string's deflection was accurate, and skin resistances were kept low to avoid overshooting.

LITERATURE

In an earlier paper,[1] the work of previous observers was briefly reviewed. It was pointed out that pain induced either by exercise or by oxygen want is an unreliable index of coronary insufficiency, partly because it represents a subjective end point, and also because so many complex factors are concerned in its production. Besides, many patients with disease of the coronary arteries do not experience pain. An objective index of effect is desirable. For this purpose, changes in the electrocardiogram following standard exercise tests have been employed by numerous workers, with positive results in cases of coronary insufficiency. It is difficult to secure reliable electrocardiograms during or immediately after exercise, particularly if four leads are taken; and encouraging patients to exert themselves to the point of discomfort is not entirely without hazard. Tests carried out with the rebreathing method do, indeed, produce alterations in the form of the electrocardiogram,[5, 6, 7] but the percentage of oxygen which is finally reached in the mixture is not fixed, so that accurate comparisons of the effect on the same person at different times, or on different persons, cannot be made.

The observations which are most nearly comparable to those here reported were made by Larsen,[8] who discussed them in an excellent monograph, published in Danish, in 1938. An eleven-page summary is given in English. He permitted patients to breathe a 9 per cent oxygen mixture, prepared by mixing a known amount of atmospheric air with a known amount of nitrogen. The mixture was inhaled for from three to eight minutes. In normal persons the changes in the electrocardiogram were very similar to those here reported. Larsen regarded as abnormal the appearance of diphasic or negative T waves in Lead I, and depression of the S-T segments more than 1 mm. below the isoelectric line in any lead. No precordial lead was employed. In thirteen of seventeen cases in which the diagnosis was "coronary angina pectoris," significant electrocardiographic changes were induced by oxygen want. In nine of these, abnormalities in the tracings were found prior to the test. The changes described were depression of the S-T segments in Lead I or Lead II, or both. The T waves in Leads I and II became diphasic in seven, and of lower amplitude, although still positive, in two. Changes also occurred in the T wave in Lead III. In the other portions of the records, no alterations were found with any degree of regularity. As a rule, the changes disappeared within five or six minutes after the test was terminated.

In four cases the control electrocardiogram showed only slight deviation from the normal, and no modification was produced by anoxemia; but depression of the S-T segments and changes in the T waves appeared after exercise.

There was no constant relationship between the occurrence of pain and electrocardiographic alterations; some patients showed a positive test without pain; others felt pain and showed no graphic changes.

Larsen points out that the absence of an abnormal response during anoxemia does not necessarily imply that the coronary arteries are free from "stenotic lesions." He speculates as to the reasons for this and suggests that perhaps under such circumstances there are lesser degrees of coronary narrowing than are present in those patients who show an abnormal response.

Ten patients over 40 years of age who complained of attacks of pain in the chest and had no objective signs of cardiac disease showed no abnormal changes in the electrocardiogram during anoxemia, but two stated that they felt their customary pain in the chest while the test was being made. It is Larsen's belief that, technically, the anoxemia test offers certain advantages over the exercise test; on the other hand, the exercise test gives a positive result a little more often. He expresses the opinion that every patient who applies for disability claims or social aid because of attacks of pain in the chest is entitled, in case of doubt, to be examined in one or both of the ways just mentioned.

In anemia, he found, as did we,[1] changes similar to those observed in coronary insufficiency caused by coronary sclerosis. He has done the

test in a number of other conditions which are not relevant to this discussion. He concludes that the method is suitable for clinical use and should be carried out under the direction of a physician; and that, when conducted properly, there is no risk to the patient.

The recent experiments of Leslie, Scott, and Mulinos[9, 10] on cats lend support to our observations on patients. After ligation of a coronary branch, characteristic deviation of the RS-T segments invariably appeared in the electrocardiogram. In one group, these changes disappeared in twelve to thirty-two days, but could be reproduced temporarily by having the animals breathe a 10 per cent oxygen mixture. In another group, persistent RS-T deviation after arterial ligation was accentuated by the induction of anoxemia.

MATERIAL

In order to establish criteria for the changes in the electrocardiogram which are induced by anoxemia in normal subjects, 115 persons without symptoms or signs of cardiac disease were tested 122 times. In the course of these tests, 976 electrocardiograms were made. The ages of these normal subjects ranged from 21 to 78 years.

TABLE I

MATERIAL STUDIED

	NUMBER OF CASES	NUMBER OF EKGS TAKEN	NUMBER OF TESTS
Normals	115	976	122
Patients	147	1340	204
Totals	262	2316	326

TABLE II

AGE AND SEX DISTRIBUTION

AGE GROUPS	NORMALS		PATIENTS	
	MALE	FEMALE	MALE	FEMALE
21–30	47	6	1	0
31–40	12	2	8	5
41–50	17	2	32	17
51–60	13	8	33	13
61–70	4	1	27	8
71–80	1	2	1	1
Totals	94	21	102	44

(Age of one man not recorded.)

In 147 cases of suspected or manifest cardiac disease caused by coronary sclerosis or hypertension, 204 tests were done, in the course of which 1,340 electrocardiograms were taken. The age range was the same as in the normal group, although the distribution in the various decades was not identical. Obviously, it was easier to find normal subjects in the younger age groups; and patients with coronary sclerosis were more numerous after the age of 40 years. There was the usual predominance of males among the cardiacs, and this relative preponderance was maintained in the normals (Tables I and II).

The patients were classified entirely on the basis of clinical observation before the anoxemia test was carried out. The form of the electrocardiogram and the size

of the heart, as measured in the teleroentgenogram, were included in the examination. The patients who were grouped under the caption "coronary sclerosis suspected" comprised those with a history suggestive of anginal pain, but with no signs of cardiac disease and with a normal electrocardiogram. The patients with "coronary sclerosis without pain" showed either an abnormal electrocardiogram or cardiac enlargement, or both. In some of these cases, previous cardiac infarction was known or believed to have occurred. Similar signs were present in the group labelled "coronary sclerosis with pain"; and among these patients, too, there were some with healed infarcts. Of the nineteen patients with "hypertension," nine had normal electrocardiograms, and ten showed changes which were not regarded as indicative of coronary sclerosis. None of the hypertensives were considered, clinically, to be suffering from coronary insufficiency.

CRITERIA INDICATING CORONARY INSUFFICIENCY

It was pointed out previously that, in normal persons, during induced anoxemia, the T waves tend to decrease in amplitude.[1] There may also be partial or complete reversal in the direction of T in Lead II or Lead III, or both. It is known that emotion, especially fear, may affect the form of the electrocardiogram. Among others, Rühl[11] and Mainzer and Krause[12] have shown that, under such stress, changes sometimes occur in both T waves and RS-T segments. That this should be so is not surprising, for, according to Cannon,[13] emotions cause a discharge of epinephrine; and this, in turn, increases the rate and work of the heart. Epinephrine also is known to produce alterations in the caliber of the coronary vessels, as well as changes in the form of the electrocardiogram.[14, 15] In a number of our subjects who were regarded as normal, and especially in the younger age groups, changes in the electrocardiogram were observed during the first test which were not present, or were of lesser degree, when the test was repeated. Presumably, the apprehension which was felt because of the novelty of the experience was absent the second time. Variations in the effects of anoxemia on the electrocardiogram may also be caused by differences in the depth and rate of respiration during any one test, or in the same person at different times. As a result, the degree of anoxemia which is induced is probably not always the same. In an earlier study,[2] in tests with a mixture containing 12 per cent oxygen, it was shown that there was no constant relationship between the time of occurrence of anginal pain and the level of arterial oxygen unsaturation. Observations correlating this level with the appearance of electrocardiographic changes have not yet been made.

The criteria for an abnormal response were made sufficiently rigid so that normal subjects who showed such variations were excluded from the group with coronary insufficiency. We have thought it wiser, for the present, to err in allowing for a relatively wide range of normal, rather than mistakenly to label as "positive" certain doubtful, borderline tests. It was perhaps on this account, as will be apparent presently, that the percentage of positive tests among the patients with coronary disease was not higher.

Criteria of an Abnormal Response.—Judging from our experience to date, the test should be considered positive when any one of the following is observed:

1. The arithmetic sum of the RS-T deviations in all four leads (I, II, III, and IVF) totals 3 mm. or more.

2. There is partial or complete reversal of the direction of T in Lead I, accompanied by an RS-T deviation of 1 mm., or more, in this lead.

3. There is complete reversal of the direction of T in Lead IVF, regardless of RS-T deviation.

4. There is partial reversal of the direction of T in Lead IVF, accompanied by an RS-T deviation of 1 mm., or more, in this lead.

The change most frequently noted was criterion 1, which occurred as the only sign in thirty-two of eighty-eight positive tests. Next in the order of frequency were combinations of criteria 1, 2, and 4; 1 and 3; and 1 and 4, which occurred 13, 11, and 10 times, respectively. Criterion 3 occurred as an isolated change eight times. All four criteria were never encountered together in the same case. Examples of the various types of change are shown in Figs. 3 and 4.

TABLE III

INCIDENCE OF POSITIVE TESTS AND OF PAIN IN VARIOUS CLINICAL GROUPS

	CONTROL EKG	TOTAL NO. OF CASES	CASES IN WHICH TESTS WERE POSITIVE			PAIN DURING TEST	
			NUMBER	PER CENT	COMBINED PER CENT	NUMBER	PER CENT
Coronary sclerosis suspected	Normal	33	6	18	18	12	28
Coronary sclerosis without pain	Normal	5	1	20	31	2	10
	Abnormal	17	7	41			
Coronary sclerosis with pain	Normal	24	10	42	55	46	63
	Abnormal	49	34	69			
Hypertension	Normal	9	0	0	5	1	5
	Abnormal	10	1	10			
Totals		147	59			61	

RESULTS (TABLE III)

Coronary Sclerosis Suspected.—Of thirty-three subjects, six, or 18 per cent, gave a positive test. In twelve cases, or 36 per cent, pain occurred during the test. Pain, in this group, was more often induced than were changes in the form of the electrocardiogram.

Coronary Sclerosis Without Pain.—This group was divided into two categories. In the first, the control electrocardiogram, which was taken before the test, was normal; in the second, it was abnormal. By abnormal it is meant that significant T-wave negativity, bundle branch

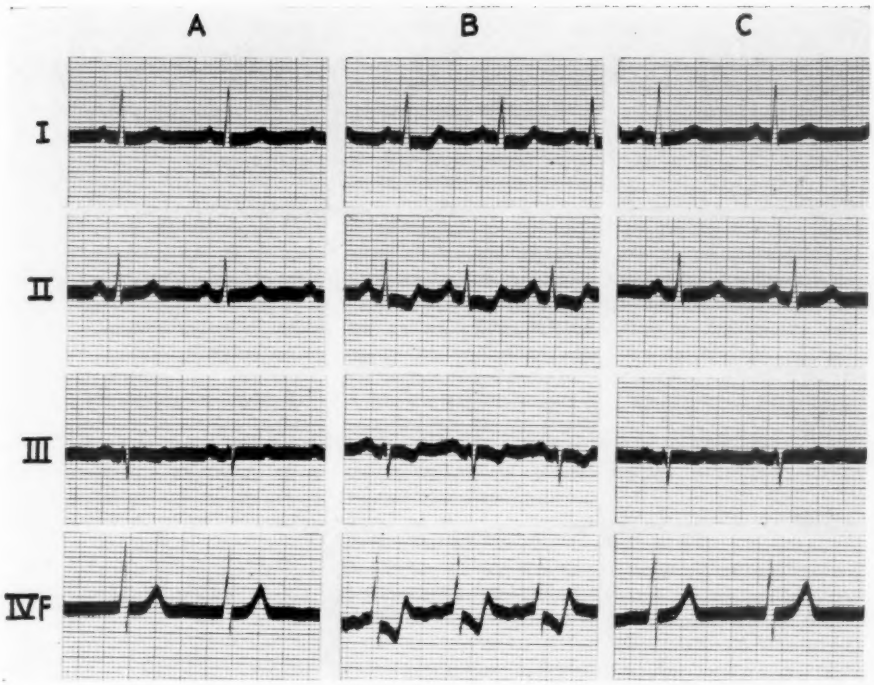

Fig. 3.—Male, aged 48 years, had coronary sclerosis with pain. Test was positive; criteria 1 and 4 present. *A*, Control. *B*, After thirteen minutes of anoxemia; pain. *C*, Five minutes after 100 per cent oxygen had been given for one minute.

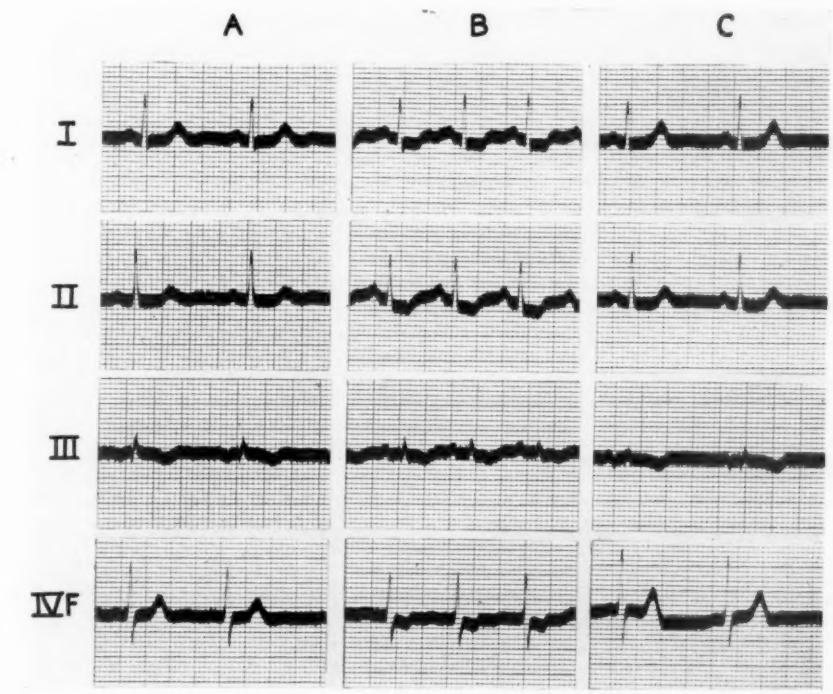

Fig. 4.—Female, aged 54 years, had coronary sclerosis with pain. Test was positive; criteria 1, 2, and 3 present. *A*, Control. *B*, After twenty minutes of anoxemia; no pain. *C*, Five minutes after 100 per cent oxygen had been given for one minute.

block, changes in the level of the RS-T segments, or combinations of these were present. Of five subjects in the first category, only one, or 20 per cent, showed a positive test. Of seventeen in the second category, seven, or 41 per cent, showed a positive test. An abnormal control electrocardiogram probably indicates more extensive impairment of the coronary bed, so that a higher percentage of positive tests might have been anticipated. Of twenty-two subjects in the group as a whole, 31 per cent showed a positive test and only two, or 10 per cent, experienced pain.

Coronary Sclerosis With Pain.—Of twenty-four patients with normal control electrocardiograms, ten, or 42 per cent, showed a positive test. Of forty-nine with abnormal control electrocardiograms, thirty-four, or 69 per cent, showed a positive test. Again, those with abnormal control records showed the higher incidence of positive tests. In the group of seventy-three subjects, as a whole, 55 per cent showed positive tests, and 63 per cent experienced pain.

Hypertension.—Of nine patients with a normal control electrocardiogram, none showed a positive test. Of ten patients with an abnormal control electrocardiogram, only one showed a positive test; and this same patient experienced pain. It should be recalled that cases of hypertension in which there was clinical evidence of coronary sclerosis were excluded. In one instance it appears that the clinical diagnosis, in this respect, was incorrect.

All Groups.—The heart rate rose 10 beats, or more, in almost all cases during anoxemia. In only two cases did the rate fall; in a small number there was no change. In a majority of the cases (64 of 113 tests, or 56 per cent) there was a rise in systolic blood pressure of more than 10 mm. Hg. In a few the pressure fell; in about one-third there was a change of less than 10 mm. Hg. The trend of the heart rate and blood pressure bore no relationship to the outcome of the test or to the occurrence of pain. All combinations of these factors were encountered.

There was no demonstrable relationship between the size of the heart and the occurrence of a positive test.

REACTIONS TO THE TEST

All of the patients became moderately cyanotic; the degree of cyanosis varied. In a previous paper,[1] two cases of pulmonary edema which occurred during the test were described. Early in the course of the present study, one additional case was observed. All three recovered promptly following a hypodermic injection of morphine and rest in the overnight ward. Including our work on drugs, part of which has already been published,[3, 4] we have performed the test over 600 times, and have encountered this untoward reaction on only these three occasions. Troublesome effects have been avoided by observing three simple rules:

1. The test should never be performed in the presence of congestive heart failure.

2. It should not be performed within 4 months after cardiac infarction.

3. It should not be done on the same patient more than once in twenty-four hours.

Unpleasant effects have been observed twenty-four times in seventeen cases; of these subjects, five were normal persons and twelve were patients with coronary sclerosis.

A. *Vasovagal reactions.*—These occurred twelve times in eleven cases, and were characterized by subjective sensations usually described as "faintness." This was accompanied by slowing of the pulse rate, fall in blood pressure, coldness of the skin, pallor, and sweating. These manifestations varied in degree from slight discomfort to a state of extreme weakness. Usually, however, the reaction was mild because its onset was recognized, the test was discontinued, and 100 per cent oxygen was promptly given. Minor T-wave variations at the height of the reaction were common. "Positive" changes appeared only twice; in both instances, with the onset of the attack, they disappeared. In one of these cases, A-V nodal rhythm replaced the sinus mechanism during the attack; in the other, A-V conduction time was prolonged temporarily from 0.15 to 0.24 second.

The attacks, in their manifestations, indicated disturbance of both vagus and sympathetic systems. That both of these, as well as the carotid sinus reflex, may be affected by anoxemia has been convincingly shown by Gellhorn and Lambert.[16] The clinical picture is similar to that described by Lewis[17] as "vasovagal syncope," except that fainting did not occur. Its failure to appear may have been caused, in part, by the fact that the patients were recumbent, and, in part, by aborting the attack with pure oxygen. Graybiel, et al.,[18] have described a similar "fainting" type of reaction during the inhalation of a 12 per cent oxygen mixture in a case of hypertensive heart disease and slight secondary anemia. In this case, after breathing the mixture for five minutes, there was a sharp fall in pulse rate and in systolic and diastolic blood pressures; pallor and cyanosis were followed by syncope.

B. *Convulsive seizures.*—These were observed twice. They were mild and lasted less than one minute. In one instance, the seizure was clearly hysterical; it occurred in an emotionally unstable woman, 45 years of age, after she had breathed a 10 per cent oxygen mixture for ten minutes. The RS-T segments were not depressed, but the T waves decreased slightly in amplitude. The attack was characterized by rigidity and tremors of the muscles, without hyperreflexia or hyperventilation. Both the pulse rate and blood pressure rose. The second patient was a 44-year-old negro, who, after five minutes of anoxemia, developed a clonic convulsion and positive electrocardiographic changes. There occurred,

in sequence, pallor of the mucous membranes, tachycardia, and syncope, but there was no significant alteration in blood pressure. Both patients recovered completely within a few minutes.

C. *Hyperventilation.*—This was observed seven times in two cases. There was no associated change in pulse rate or blood pressure. In one case, pain was experienced without electrocardiographic changes. The second patient, who had a healed cardiac infarct, reacted in this fashion on six different occasions; four positive tests were followed by two negatives. The latter were obtained after clinical improvement had taken place.

D. *Dyspnea.*—In two tests on a 59-year-old white man, whose electrocardiogram showed left bundle branch block, pain developed; at the same time, his respirations became deep and labored. Anoxemia had to be discontinued after five minutes on one occasion, and after eleven minutes the second time. Both tests were negative, probably because the duration of anoxemia was too short. There was no change in pulse rate or blood pressure.

E. *Mental confusion.*—This was observed once in the case of a 74-year-old woman with manifest cerebral arteriosclerosis. It lasted less than fifteen minutes. In the previous series of cases[1] this was recorded as a transient occurrence in two cases, in both of which the patient was believed to have sclerotic cerebral vessels.

None of these reactions was serious or harmful. The vasovagal seizures were disturbing until we became familiar with them. If the test was promptly stopped when pallor, sweating, coldness of the skin, or marked slowing of the pulse rate was noted, and 100 per cent oxygen was given promptly, the attack could be aborted. Patients who show any of these types of reaction during the first test should not be subjected to the procedure a second time. We repeated the observations six times in the case of the subject who hyperventilated because he did not object and did not appear to suffer any ill effects.

COURSE AND NECROPSY PROTOCOLS OF PATIENTS WHO SUBSEQUENTLY DIED

Of the 147 patients, nine have died. Death occurred from four weeks to twenty-one months after the last test was done. Five of the nine patients died suddenly. On one of these five, the test was done twenty-one months prior to death, but had to be discontinued at the end of seven minutes because of a paroxysm of coughing. No electrocardiographic changes had appeared at this time, although the man was known to have a healed myocardial infarct. The other four patients in this group showed positive tests.

The test was negative on one patient with hypertension. He died at home, of congestive heart failure, five months later. One patient with a positive test died three months afterward, of coronary occlusion.

Necropsy was performed in two cases. Brief abstracts of the clinical and pathologic records follow.

CASE 1.— F. B., Unit No. 402171. A white man, aged 67, complained of dyspnea on exertion and precordial oppression of six weeks' duration. The heart was a little enlarged to the left. The blood pressure was 152/84. An electrocardiogram showed right bundle branch block and prolonged A-V conduction. The P-R interval measured 0.22 second; the QRS interval was 0.11 second. There was no anemia. The diagnosis was coronary sclerosis.

Because of persistent epigastric discomfort, roentgenologic studies of the gastrointestinal tract were made. These showed carcinoma of the antral portion of the stomach. An operation was performed, and the patient died five days later of type III pneumococcus pneumonia. The organism was recovered in the blood culture.

An anoxemia test was done 2½ months before death, and was positive (Fig. 5).

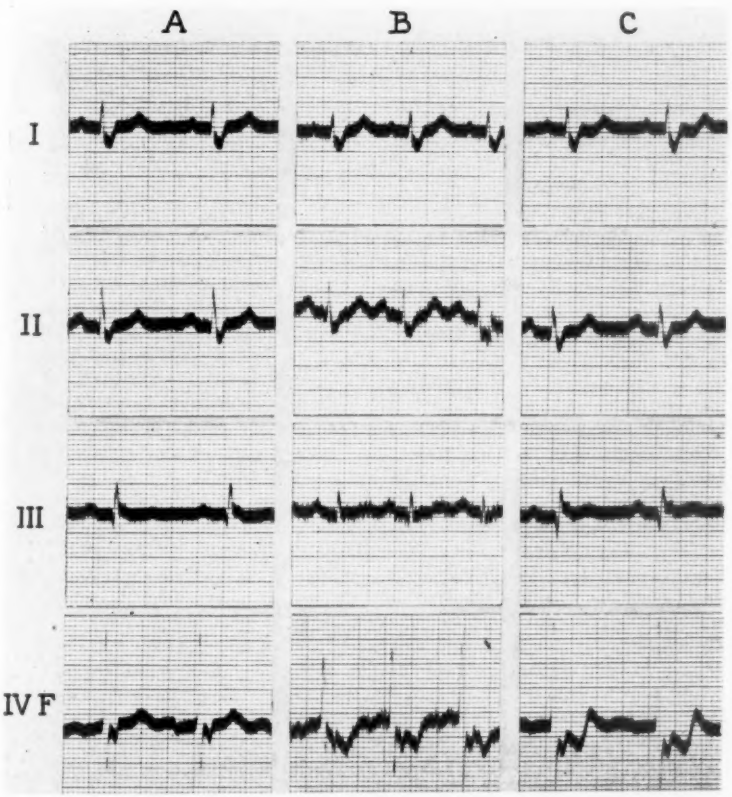

Fig. 5.—Case 1. Male, aged 67 years, had coronary sclerosis with precordial oppression for six weeks. Test was positive. Operation for carcinoma of stomach; death from pneumonia 2½ months after test. Necropsy showed narrowing of circumflex branch of left coronary artery and widespread fibrosis of posterior wall of left ventricle. *A*, Control. *B*, After ten minutes of anoxemia; pain. *C*, Immediately after one minute of 100 per cent oxygen.

*Necropsy.**—The heart weighed 400 grams. The walls of both coronary arteries showed numerous atheromatous plaques, without calcification. The lumen of the descending portion of the circumflex branch of the left coronary was narrowed to about half its normal size. There was widespread fibrosis of the posterior wall of the left ventricle. Elsewhere, the myocardium was free from scars. Microscopic examination of the left ventricle showed numerous, large areas of dense,

*We are indebted to Dr. James W. Jobling, Director of the Department of Pathology, for permission to use the necropsy protocols.

fibrous, connective tissue. In these areas there were atrophy and disappearance of muscle fibers. Elsewhere, these fibers were normal. There was no cellular inflammatory reaction.

CASE 2.—E. P., Unit No. 453191. A white man, aged 61, had an attack of acute coronary occlusion in May, 1935, and remained in the hospital for six weeks. The electrocardiogram was characteristic of posterior myocardial infarction. He was followed in the outpatient department, where it was noted that his discomfort became progressively less. In October, 1937, he was taking only 2 nitroglycerin tablets each week.

In August, 1938, signs of congestive failure, with right-sided hydrothorax, appeared. The heart was enlarged. The blood pressure was 140/80. The electrocardiogram showed inversion of T_1, T_2, and T in Lead IVF. He improved markedly with rest and therapy.

On Dec. 29, 1939, he was operated upon for carcinoma of the ascending colon. The operation lasted over three hours, and he stood it well. He died ten days later (Jan. 8, 1940) of peritonitis resulting from rupture of the intestinal anastomosis.

An anoxemia test, done three years after the attack of coronary occlusion and 8 months before death, was negative.

Necropsy.—The heart weighed 560 Gm. There were healed infarcts involving the left ventricle and interventricular septum. The coronary arteries showed advanced sclerosis, with occlusion of the anterior descending and circumflex branches of the left coronary by calcified material. Microscopically, at the apex of the left ventricle the wall was thinner than normal. There were no fresh areas of necrosis or inflammation. The small coronary arteries were slightly sclerotic and narrowed. The wall of the left ventricle showed similar changes. There were no recent thrombi in any of the coronary vessels.

Acute, generalized, fibrinopurulent peritonitis and bilateral lobular pneumonia were the immediate causes of death.

DISCUSSION

Judging from the evidence presented, it appears that a positive anoxemia test is a sign of functional insufficiency of the coronary circulation. This term is used to mean that there is a disproportion between the need of the heart for blood and the ability of the coronary vessels to deliver an amount sufficient to meet this requirement. Such a disproportion may be brought about by any factor which diminishes coronary flow or increases the work of the heart. As with all bodily functions, there is a reserve in the coronary bed which can be drawn upon in case of need. Only when this has been exceeded do signs and symptoms of insufficiency become apparent.

The commonest cause of a diminished coronary reserve is disease of the coronary arteries; and, of these diseases, arteriosclerosis comprises over 90 per cent.[19] But there are other causes, also, such as syphilis of the aorta, with stenosis or occlusion of one or both coronary orifices; aortic stenosis or insufficiency; paroxysmal tachycardia; and anemia, in which the heart suffers from anoxemia along with the rest of the body. In this paper only cases of coronary sclerosis have been discussed. Other conditions are being studied.

The usefulness of the test as a clinical diagnostic measure can best be illustrated by presenting briefly the following history:

CASE 3.—*Coronary sclerosis suspected. Pain atypical. Test positive.*

G. A. M., a male merchant, aged 53 years, complained of substernal pain of ten days' duration. His father died at the age of 65 of heart disease; his mother was over 90 years old. His health had been excellent. He was a hard worker, with large business responsibilities, and took almost no exercise. He smoked sixty cigarettes and drank four cups of coffee daily. His family physician had requested an electrocardiogram two years previously because he suspected that the patient had a "tired heart."

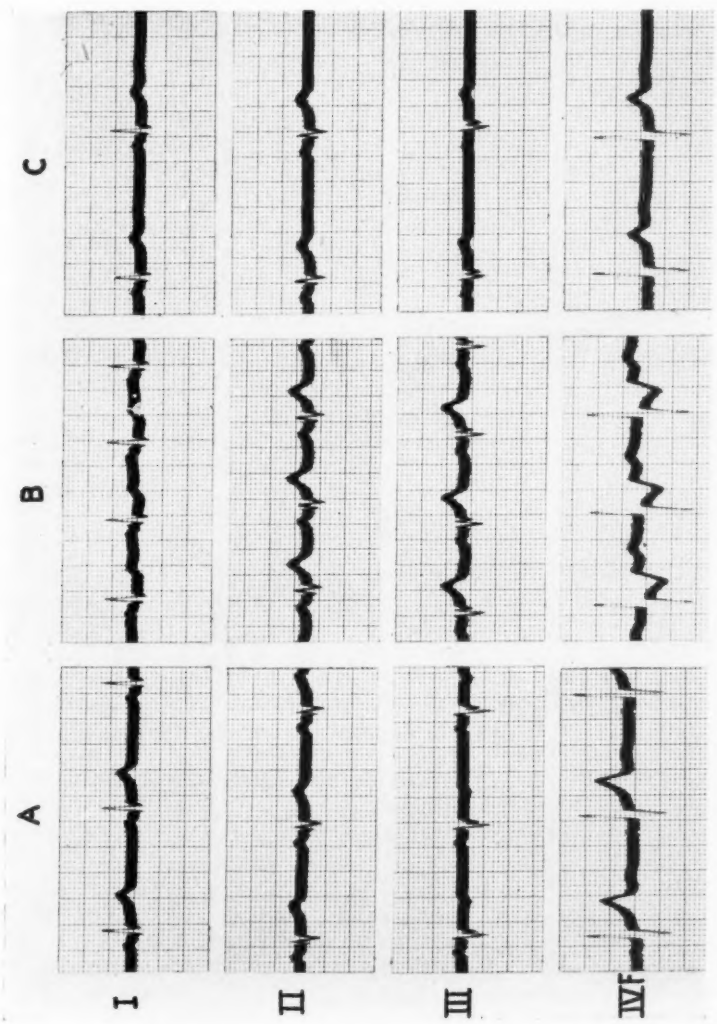

Fig. 6.—Case 3. Male, aged 53 years. Coronary sclerosis suspected; examination negative. Test was positive. *A*, Control. *B*, After ten minutes of anoxemia; pain. *C*, After one minute of 100 per cent oxygen.

Ten days before his visit he began to experience substernal pain which radiated to the back of the neck and to both arms, and usually occurred in the middle of the night. This recurred at intervals, and, according to his story, was unaffected by nitroglycerin. There was no discomfort during the day's activities. There was no dyspnea.

Examination showed that he was not overweight. There was no retinal or peripheral sclerosis. The heart was normal in size, as shown both by percussion

and orthodiagraphic measurement. The rhythm was normal, the rate, 64. The sounds were normal and clear. The blood pressure was 132/80. The electrocardiogram showed only left axis deviation.

It was the impression of the examiner that the patient suffered from nervous tension, as well as from poisoning by coffee and tobacco. He appeared to need a vacation. The anoxemia test was strikingly positive (Fig. 6).

He was seen again six months later. He was working less, and, on two evenings a week, retired at 6 o'clock, taking supper in bed. The discomfort continued at night for a time, but gradually became less marked. He noted upper sternal pressure on walking home from business, although there was no discomfort in the mornings when he was not tired. Emotional reactions also caused pain. Nitroglycerin, he now reported, gave relief. The electrocardiogram at this time was similar to the one taken previously.

He reported again eleven months after the first visit and stated that he was greatly improved. There was still some discomfort on walking when he was tired. Also, occasionally, after a heavy dinner, he had slight pain in the chest which radiated down the left arm. He required nitroglycerin rarely and irregularly, going sometimes for several months without it. During the entire eleven months, he took a capsule containing 3 grains of aminophyllin and ¼ grain of phenobarbital three times a day.

The control electrocardiogram at this time was similar to those taken previously, except that the T wave in Lead III was upright. The anoxemia test was negative.

In this case, objective evidence of coronary sclerosis, obtained by the test ten days after the onset of symptoms, made possible a definite diagnosis. As a result of material modification in his mode of life there was progressive improvement. Increase in the functional capacity of the coronary circulation was demonstrated by the anoxemia test.

The test has also been used to follow the healing of an area of infarction. The electrocardiographic pattern gives a graphic picture of the development of an adequate collateral circulation, even when the control electrocardiogram remains unchanged. The following case is illustrative.

CASE 4.—*Coronary occlusion with cardiac infarction, followed by gradual lessening of symptoms. As the clinical condition improved, the anoxemia test, which was at first positive, became negative.*

W. T. D., Unit No. 568485. A male post office employee, aged 48 years, was admitted to the hospital March 18, 1939, complaining of attacks of substernal pain for one week. Two years previously he had been in bed for a month with what was called myocarditis. He had since had occasional, mild, substernal pain, which was unrelated to effort or meals. Nine days before admission he suffered an attack of substernal oppression which lasted two days, this time with radiation to the neck, left shoulder, and arm, and accompanied by syncope, nausea, and vomiting.

The clinical picture was typical of coronary occlusion. The electrocardiogram showed prolonged conduction, with a P-R interval of 0.33 second; T_2 and T_3 were inverted, and Q_3 was large; these changes indicated posterior infarction. There was fever for a week. The erythrocyte sedimentation rate returned to normal on the eighth day after admission. Convalescence was uneventful.

Three months after the attack a teleroentgenogram showed a slight increase in the transverse diameter of the heart. He was having twinges of pain on effort. Five months after the attack there was still some heaviness in the precordium when he first went out in the morning. The blood pressure was 120/80. The anoxemia test at this time was positive (Fig. 7, *A* and *B*). There was gradual improvement,

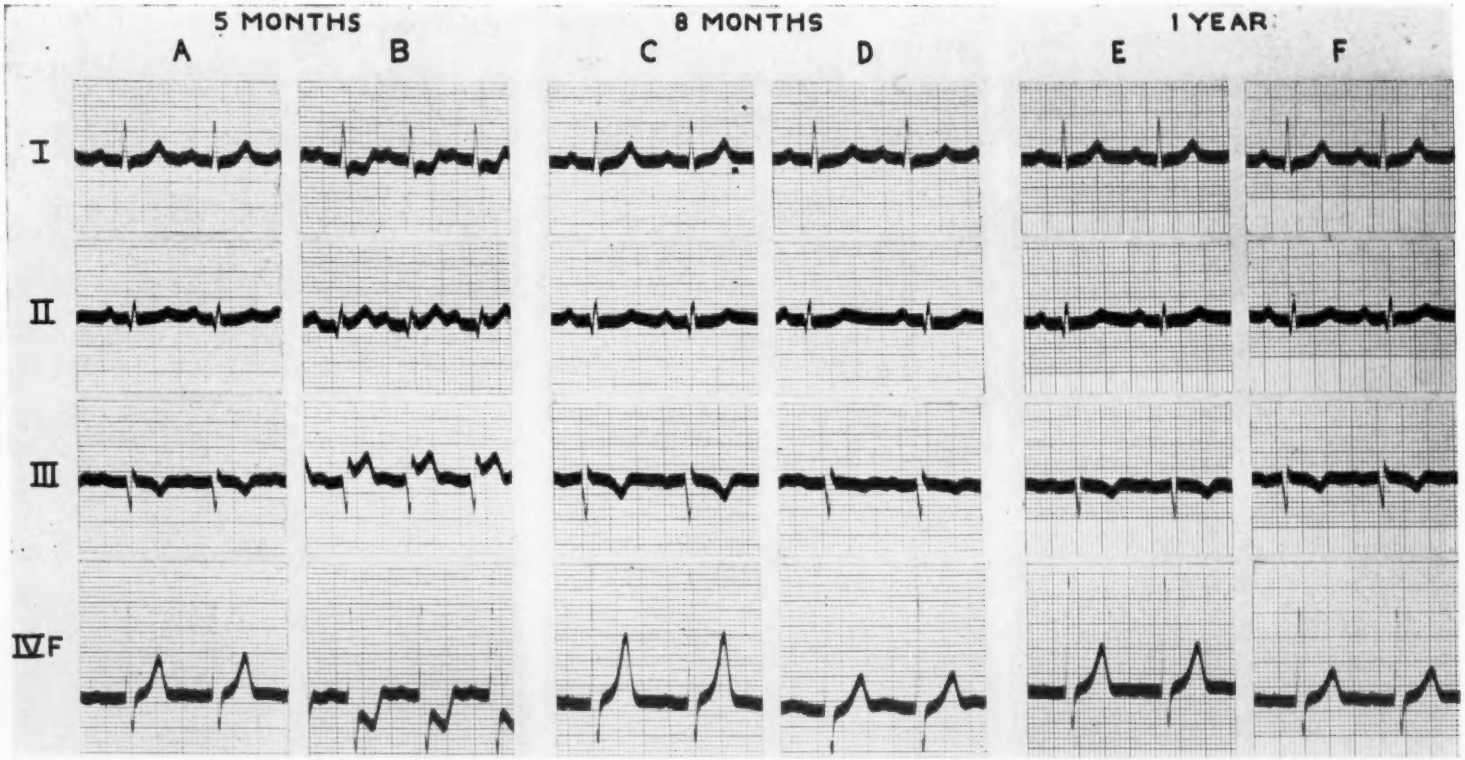

Fig. 7.—Case 4. Male, aged 48 years. Coronary occlusion with cardiac infarction. Positive test, becoming negative coincident with clinical improvement. Five months after attack: Still having paroxysms of pain; test positive. *A*, Control. *B*, After eighteen minutes of anoxemia; pain. After eight months: no discomfort; test negative. *C*, Control. *D*, After twenty minutes of anoxemia; no pain. After one year: working full time; test negative. *E*, Control. *F*, After twenty minutes of anoxemia; no pain.

with disappearance of all discomfort at the end of eight months. At this time the anoxemia test was negative (Fig. 7, *C* and *D*). A year after the attack of coronary occlusion he was working full time at his old job and had no complaints. The blood pressure was 125/70 (Fig. 7, *E* and *F*).

It is apparent (Table III) that, in a considerable number of cases, a negative test was obtained when symptoms and signs suggested the presence of coronary sclerosis. In some of these cases, later tests, taken when the pain was more frequent and intense, gave a positive result. In three cases, in all of which there were healed infarcts of the myocardium, both positive and negative tests were obtained at different times, within a few months, without demonstrable change in the clinical status. The explanation for this is not entirely clear, but it is possible that in such cases the margin of coronary reserve is small; relatively slight factors, such as emotional upsets, indigestion, or an added burden of work, may suffice, on occasion, to decide the balance. Probably, also, organic changes which are not accompanied by symptoms occur in the coronary circulation from time to time. One patient with a typical history of anginal pain, but with a negative physical examination and anoxemia test, suffered an attack of coronary occlusion eleven months after his visit to the clinic. This was an instructive experience and is here briefly told.

CASE 5.—A. W., Unit No. 409247. The patient was a plumber, aged 43 years. His symptoms had begun six months previously (July, 1938), with pain in the precordium and dyspnea on exertion. He had never been seriously ill. The pain began with a feeling of pressure under the sternum and radiated to the left axilla. There was progressive shortness of breath on effort.

Percussion showed that the heart was normal in size. The sounds were loud and clear. The blood pressure was 128/74. A teleroentgenogram showed a slight increase in the cardiothoracic ratio. The blood cell count was normal. The Kline test on the blood was negative. An electrocardiogram showed left axis deviation; T_3 was inverted; R-T_1 was slightly elevated; and the precordial lead was normal. An anoxemia test on March 22, 1939, was negative. Shortly after the start of the test the patient complained of mild retrosternal pressure, and, at the end of eighteen minutes, experienced slight pain. However, this disappeared quickly, and he completed the full twenty minutes of anoxemia. He stated that the discomfort was similar to that which occurred spontaneously, and was accompanied by slight nausea.

He was followed in the outpatient clinic, and was thought to be able to do ordinary work. On Jan. 15, 1940, he had an attack of acute coronary occlusion, according to his physician. An electrocardiogram which was made at the Presbyterian Hospital on Feb. 26 (six weeks later), confirmed the diagnosis; T_2 was diphasic and T_3 and T in Lead IVF were inverted. The erythrocyte sedimentation rate at this time was 15 mm. in one hour.

There are at least five reasons why there may be a discrepancy between the clinical diagnosis and the result of the anoxemia test: (1) The clinical diagnosis was incorrect. (2) The criteria employed were sufficiently rigid to exclude borderline cases. (3) The area of the heart affected by

the coronary lesions was "silent" with respect to electrocardiographic changes caused by anoxemia. Following infarction of the lateral wall of the heart, the resting electrocardiogram may show only minor and transitory alterations in form.[20] (4) The coronary lesions were early and slight; the coronary flow was not reduced sufficiently to register changes under the conditions of the test (Case 5). Larsen[8] has called attention to cases in which there were a negative anoxemia test and a positive reaction to exercise. (5) After infarction, an adequate collateral circulation may be established, so that, actually, coronary insufficiency does not exist[21] (Cases 2 and 4).

It is apparent, then, that a positive anoxemia test is a sign of coronary insufficiency and indicates a *diminished coronary reserve.* So far, no other clinical condition has been found to be associated with similar changes in the electrocardiogram. A negative test, however, does not exclude the presence of coronary lesions or of a healed myocardial infarct.

The test is simple and safe. It has proved to be of diagnostic value in distinguishing pain of coronary origin from that due to other causes. It has been employed to study, in patients, the effect of various drugs on the coronary circulation. It affords a graphic method of recording the efficiency of the coronary circulation at varying intervals after coronary occlusion. It is suggested that it may be employed as a measure of the effectiveness of the establishment of collaterals in the coronary bed after surgical procedures designed to promote their formation. It should prove useful in the examination of patients who claim disability benefits because of anginal pain, and in insurance examinations when coronary sclerosis is suspected. Only a positive result should be regarded as significant.*

SUMMARY

1. Using an apparatus and a technique previously described, anoxemia tests were performed on 115 normal persons and 147 patients with suspected or manifest cardiac disease. In all, 326 tests have been carried out on 262 subjects, in the course of which 2,316 electrocardiograms were taken.

*Since this paper was written and presented, Riseman and his collaborators have reported their experience with "electrocardiographic changes during generalized anoxemia as a diagnostic criterion of angina pectoris or coronary artery disease" (Riseman, J. E. F., Waller, J. V., and Brown, M. G.: The Electrocardiogram During Attacks of Angina Pectoris; Its Characteristics and Diagnostic Significance, AM. HEART J., 19: 683, 1940). Observations were made on five patients with angina pectoris and eight normal subjects, who were allowed to breathe an atmosphere containing "approximately" 10 per cent oxygen for ten minutes, or until pain was felt. There were no untoward effects. Only the precordial lead was used, and in each group this was recorded by a different technique. In the patients with angina the tracings were taken according to the old method, using the apex and left arm; in the normal subjects, they were taken according to the newer technique, using the apex and right arm (Lead IVR). Accurate comparison between the two sets of records was obviously impossible.

It was concluded that "changes in the electrocardiogram during generalized anoxemia appear to be of little practical value in differential diagnosis, for the difference between the normal and abnormal responses is not sufficiently marked to avoid serious error; and that, judging from the literature, the induction of generalized anoxemia is not without danger." In view of the limited number of observations and the manner in which these were carried out, further comment is unnecessary. The questions raised by the conclusions are answered fully in the body of our paper.

2. In normal persons, the changes in the form of the electrocardiogram during anoxemia are relatively slight. There is usually lowering of the amplitude of the T waves in all of the four leads. There may be inversion of the T wave in Leads II and III.

3. Criteria have been established for an abnormal response. These criteria are sufficiently rigid to exclude alterations in the form of the electrocardiogram which may occur as the result of emotion or other spontaneous variables.

4. The test was positive in 18 per cent of 33 patients with suspected coronary sclerosis; in 31 per cent of twenty-two patients with coronary sclerosis but no history of anginal attacks; in 55 per cent of seventy-three patients with coronary sclerosis and a history of anginal attacks; and in only 5 per cent (one case) of nineteen patients with hypertension without symptoms or signs of coronary sclerosis. Patients whose control electrocardiogram was abnormal showed a higher percentage of positive tests than those with a normal control tracing. The highest incidence of positive tests was obtained in a group of forty-nine patients with anginal pain caused by coronary sclerosis and abnormal control electrocardiograms; in 69 per cent of these an abnormal response was obtained.

5. There was no relationship between the size of the heart and the incidence of positive tests.

6. There was no constant effect on pulse rate and blood pressure.

7. There was no constant relationship between the occurrence of a positive test and the appearance of pain during anoxemia.

8. No serious untoward effects were observed, provided the test was not carried out when congestive failure was present, was not done more than once on the same patient within twenty-four hours, and was not made before the lapse of four months after an attack of coronary occlusion.

9. Unpleasant reactions were encountered twenty-four times in seventeen cases. These were classified as vasovagal attacks, convulsions, hyperventilation, dyspnea, and mental confusion. None of these reactions was serious or harmful.

10. Nine of the patients in the group died at varying intervals following the test. Necropsies were performed on two. In one case in which the test had been positive, narrowing of the circumflex branch of the left coronary artery and widespread fibrosis of the posterior wall of the left ventricle were found. The heart of the second patient, who had had an attack of coronary thrombosis 5 years before his death from postoperative peritonitis, showed old occlusion of the anterior descending and circumflex branches of the left coronary artery, with healed infarcts of the heart. In this case, the anoxemia test, done eight months before death, was negative.

11. A negative test does not rule out the possibility of early coronary lesions or of healed cardiac infarction. Some of the reasons for the high incidence of negative tests in cases of suspected or known coronary sclerosis have been discussed.

12. The test is simple and safe. When positive, it is a sign of coronary insufficiency and indicates a diminished coronary reserve.

13. The test has proved to be of diagnostic value in distinguishing pain of coronary origin from that due to other causes. It has been useful in affording a graphic record of the efficiency of the coronary circulation at varying intervals following coronary occlusion. It has afforded a method for studying, in patients, the effect of various drugs on the coronary circulation.

14. It is suggested that it may be employed as a measure of the effectiveness of the establishment of collaterals in the coronary bed following surgical operations designed to promote their formation.

15. It may prove useful in cases in which disability is claimed because of anginal pain, and also in insurance examinations when coronary sclerosis is suspected.

16. Only a positive result should be regarded as significant.

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DISCUSSION

DR. CLOUGH T. BURNETT (Denver).—I want to congratulate Dr. Levy on his paper and his very excellent slides. In Denver, my associates and I have been much interested in this subject. We felt that it was worth while to repeat Dr. Levy's work for two reasons. We live at an altitude of a mile above sea level, and felt that this might have a profound effect upon the results of the test because, in the earlier work of Dr. Levy, age was not given so much consideration.

We have done more than 120 tests. Most of these were on normal young adults between the ages of 20 and 40 years, but a few of the subjects were more than 40 years old.

Our criteria for the normal (and we have attempted so far as possible to work with the normal) have been essentially those of Dr. Levy.

We have noted some points that are of interest. For example, we have checked the pulse pressure, which was not mentioned this morning by Dr. Levy, but was in an earlier paper. We do not feel that these changes can be considered significant, and, in all of the tests, such changes as we have encountered contradict the contention that this test involves an undue strain on the subject.

All of those associated in this investigation have taken the test several times, but never twice on the same day. One of us has taken it four times. Under proper control we consider it safe.

We noticed progressive cyanosis of the fingertips. We would like to work out some means to standardize this. So far we have not. During the first few minutes of the test there is moderate air hunger, which shortly disappears. Any tendency to fear at the beginning naturally gives false control blood pressure and pulse rate levels, and this is misleading because these values may be lower at the end of the test than before it was begun.

Dr. Levy mentioned some unpleasant experiences. We had two such experiences on the same day, and, unfortunately, with two of our older colleagues. We found that this was caused by an unrecognized error in the composition of the oxygen-nitrogen mixture. In this case we were working with an 8.6 per cent oxygen content, which is too low for safety. These subjects found that the test was intolerable, and it had to be discontinued.

Dr. Levy mentioned syncope. As I understood him, he said that it hadn't occurred. We had two cases of apparent syncope on the same afternoon, with a marked reduction in the pulse rate and blood pressure. Since both of these occurred in women, and the second subject had seen what happened to the first, we regarded it as psychic in origin. These were the only occurrences of this kind in approximately 120 tests.

We found that physicians and nurses were the poorest subjects, probably again for psychic reasons. We have found, also, that giving too elaborate instructions to the subject regarding the test is probably undesirable.

There is a remarkable uniformity in the electrocardiographic pattern at the age with which we have worked. As to the older subjects, I would not care to make any comment at this time.

Dr. Levy mentioned mental confusion. We have encountered this in two instances, and one of these two subjects nearly had a convulsion. In all of these instances the undesirable effects were controlled immediately with the pure oxygen which, of course, must be available for emergencies.

Of peculiar interest to physicians who practice in the higher altitudes is the response of normal persons who have lived at sea level and travel to higher altitudes. We have made some observations on such subjects and hope to have sufficient additional observations in a few months. The usual control observations are made at sea level. Fortunately, there are two trains which run from Chicago to Denver in fifteen hours, so that the ascent of practically one mile is made in this time. Immediately on arrival the second set of observations is made, and at once the subject is taken to the highest possible altitude. In winter we have used Berthoud Pass, which has an altitude of 11,306 feet; in summer we plan to go to the summit of Mt. Evans, which is 14,260 feet above sea level. At these mountain stations a third series of observations is made, after which oxygen is administered for one minute, as in the standard test, and a fourth series of clinical and electrocardiographic records obtained. Naturally, this series is small, and we do not care at this time to make any detailed statement, but the effect of rapid change in altitude appears to be quite similar to that of artificially induced anoxemia.

At this time I wish to express our appreciation for the courtesies and cooperation extended to our group by Dr. Levy.

DR. H. R. MILLER (New York City).—I, too, found it a pleasure to hear Dr. Levy. I wonder whether he would be good enough to reconcile his results with some experimental data which we published a number of years ago, and with certain physiologic criteria which bear upon the same problem.

Together with Drs. Felberbaum and Krigel, we obtained, in healthy cats, electrocardiographic changes similar to those shown by Dr. Levy. These effects were caused by asphyxia, and they disappeared when the cats were allowed to recover.

These and similar observations raise the point whether one is dealing fundamentally with a chemical process or a nervous regulation. The possibility that there is a nervous regulation is related to the investigations of Levy, in England, and to the studies of Beattie, Brow, and Long, who demonstrated that, in cats, cardiac arrhythmias may be induced (and registered electrocardiographically) merely by putting the cat under chloroform. The effects were abolished when the efferent sympathetic fibers which descend from the diencephalon were severed. In other words, although a chemical agent, in this instance, chloroform, still acts, or, at least is still expected to be in operation, the induced effect upon the cardiac mechanism can be abolished by interrupting a nervous pathway.

Another point which seems to me of some interest revolves about any inference that blood flow (with reference to the heart, the quantity of blood received by this organ) is synonymous with the oxygen content or saturation. As far as I know, the level of oxygen concentration of the blood does not parallel the level of blood pressure in the sinuses of Valsalva. It is therefore quite conceivable that the quantity of blood which the heart will receive, under adverse circumstances or in emergencies, may be entirely adequate and the oxygen content deficient, or vice versa.

The latter point, I believe, is tied up with the important physiologic consideration that in all circumstances when the heart is threatened, whether by shock or asphyxia, or whether the coronary vessels themselves are damaged, the physiologic equilibrium of cardiovascular dynamics operates to bring more blood than ever

to the heart. This has some relevancy not only to the aspect of the nervous regulation of the circulation, especially of the coronary circuit, but is significant in the light of the recent studies of the Albany workers, Martin and Gorham. They showed that the amount of blood which can enter the irrigating vessels of the heart may be more than normal when, for example, a coronary vessel is pulled upon tridirectionally and pain is produced.

The final query I wish to bring up is whether it would not be of advantage, certainly from a clinical point of view, to separate the effects of asphyxia from those initiated as electrocardiographic changes. These two sets of effects need not be concurrent.

DR. LOUIS N. KATZ (Chicago).—Would Dr. Levy tell us how many normals there were in the older age group, i.e., those approaching senescence, as compared with the younger group? Secondly, would he use this test in preference to his own clinical judgment?

We had the good fortune to have with us M. Kissin, who, several years ago, with M. A. Rothschild, initiated the use of anoxemia as a test for angina pectoris. In collaboration with Drs. Hamburger and Schutz, Dr. Kissin and I gave the foregoing method a further trial on normals and patients with coronary disease; we were soon convinced that it was potentially too hazardous for general use, and that the distinction between normals and patients with coronary disease who had normal electrocardiograms to begin with was not always marked.

DR. ROBERT L. LEVY (New York).—I greatly appreciate Dr. Burnett's interesting discussion. Our observations on changes in blood pressure and heart rate, like his, have shown no direct relationship to the outcome of the test, that is, as to whether it was positive or negative. We have checked our oxygen mixture at frequent intervals and have found that it did not vary more than plus or minus 0.6 per cent.

Fear, it is known, causes changes in the form of the electrocardiogram. We have observed changes in normal persons during the first test which did not appear during the second. Our criteria have been made sufficiently rigid so that the changes caused by fear are covered by the range of normal variation.

Dr. Miller has referred to the mechanism of the action of anoxemia and asphyxia. I cannot take time to go into that here. It has been shown, notably by Gellhorn and his associates, that anoxemia affects both vagus and sympathetic systems, and these workers have, quite recently, published an interesting monograph on the effects of anoxia and asphyxia on the vasomotor system.

As Dr. Miller has pointed out, pain and a positive test are not necessarily associated. A positive test may be obtained without the appearance of pain, and vice versa. Sometimes both occur.

As for Dr. Katz's points, in the first place, the test that Kissin and Rothschild used was not comparable to the one we employed. I think that should be made very clear. Their patients rebreathed the same mixture; and with that method no standardization of the results is possible.

In the second place, he asked how many normals showed a positive test. Of course, no normals showed a positive test because our criteria were made up on the basis of the range of variation observed in people without heart disease.

He asked also whether it is feasible to use the test in private practice. I use it in my own office. One of the patients whose tracings were shown, in my opinion, did not have coronary sclerosis. You will recall that the physical examination and the control electrocardiogram were negative. I thought that he was working too hard, smoking too much, and going to too many night clubs. Because his test was positive, he was advised to modify radically his mode of life. His improvement, in the course of a year, was striking.

EXPERIMENTAL ATHEROSCLEROSIS

III. Electrocardiographic Studies and Pathologic Changes in the Hearts of Cholesterol-Fed Rabbits

Jan Nyboer, M.D., Maurice Bruger, M.D., and S. Milton Rabson, M.D.
New York, N. Y.

SINCE atherosclerosis was first produced experimentally about twenty-five years ago in rabbits by the feeding of cholesterol, an appreciable amount of work on the pathologic and chemical phases of the problem has been carried out in this country and abroad. As far as is known, however, there are no studies relating experimental atherosclerosis of the coronary arteries with electrocardiographic changes. An investigation of this kind appeared all the more important since clinical studies of patients with heart disease have emphasized the frequent association of coronary artery disease and abnormal electrocardiograms.

MATERIAL AND METHODS

Twelve rabbits varying in age from 3 to 4 months were obtained. Five were set aside as controls and were observed for 126 days. Purina chow was fed once daily, and water was left in the cages at all times. To the same basal diet of each of seven rabbits was added 1 Gm. of cholesterol three times a week. This group was also studied for 126 days. Electrocardiographic studies and blood cholesterol determinations were carried out at intervals of two to five weeks. The electrocardiographic studies included the usual standard leads, as well as exploratory leads from the right (V) and left (IV) chests paired with an indifferent electrode on the left thigh.

The cholesterol content of the whole blood was determined by a modified Bloor procedure.[1, 2] The method of sacrificing the animals and the technique for removal of the aorta and for the determination of its cholesterol content have been described elsewhere.[3] At necropsy, several sections were taken from the heart for microscopic study.

RESULTS

Blood Cholesterol.—The whole blood cholesterol of the control rabbits on the 126th day of observation ranged from 120 to 200 mg. per cent, and that of the cholesterol-fed rabbits from 280 to 1,210 mg. per cent (Table I).

Body Weight.—In 126 days the control rabbits gained from 255 to 636 Gm. in weight, and the experimental rabbits from 113 to 1,641 Gm. (Table I).

Cholesterol Content of the Aorta.—The cholesterol content of the aorta in the control rabbits ranged from 0.402 to 0.588 Gm., with a mean of 0.465 Gm. per 100 Gm. of dry aorta. The cholesterol content

From the Departments of Medicine and Pathology, New York Post-Graduate Medical School and Hospital, Columbia University, New York, N. Y.
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TABLE I

WHOLE BLOOD CHOLESTEROL, CHOLESTEROL CONTENT OF THE AORTA, GAIN IN BODY WEIGHT, PATHOLOGIC OBSERVATIONS OF AORTA AND HEART, AND ELECTROCARDIOGRAPHIC CHANGES IN CONTROL RABBITS AND IN RABBITS RECEIVING 3 GM. OF CHOLESTEROL A WEEK FOR 126 DAYS

RABBIT NO. AND SEX	BLOOD CHOLESTEROL (MG. %)					TOTAL GAIN IN WEIGHT (GM.)	AORTA CHOLESTEROL (GM. PER 100 GM. DRY WEIGHT)	PATHOLOGIC OBSERVATIONS		ELECTROCARDIOGRAPHIC CHANGES*		
	0 DAYS	15 DAYS	44 DAYS	85 DAYS	126 DAYS			MACROSCOPIC (AORTA)	MICROSCOPIC (HEART)	RATE	QRS VOLTAGE IN INDICATED LEADS	T VOLTAGE IN INDICATED LEADS
Control Group												
12, M	101	116	125	109	131	636	0.437	Apparently normal	Coronary arteries and myocardium without alteration	Decreased	Decreased II, III	No change
13, F	97	123	154	109	120	425	0.424	Apparently normal	Coronary arteries and myocardium without alteration	Increased	Decreased II, III, IV, V	Indeterminate
14, M	120	142	160	117	184	340	0.402	Apparently normal	Coronary arteries without alteration. Myocardium, lymphocytic foci in lateral ventricular wall	Decreased	Decreased I, V Increased III, IV	Decreased IV Increased I, II, III, V
15, F	128	188	200	204	200	623	0.473	Apparently normal	Coronary arteries and myocardium without alteration	Decreased	Decreased I, II, III, IV, V	Increased V from negative to positive
16, F	114	108	170	156	144	255	0.588	Apparently normal	Coronary arteries and myocardium without alteration	No change	Slightly decreased I, II, III	Decreased IV from positive to negative
Cholesterol-Fed Group												
1, F	128	335	938	721	833	1585	7.610	Marked atherosclerosis	Atherosclerosis of coronary arteries (interauricular and interventricular septa, left posterior papillary muscle, valvular apparatus). Myocardium without alteration	Increased	Decreased I, II, III	No change

*The P-R and QRS intervals, the electrical axis, and the RS-T segment remained unchanged throughout in both control and cholesterol-fed rabbits.

3, M	101	109	361	251	280	538	1.217	Minimal atherosclerosis	Atherosclerosis of coronary arteries (left auricle and ventricle, interauricular and interventricular septa). Myocardium without alteration	Decreased	Decreased I, II, III	No change
5, F	111	330	708	781	872	311	2.052	Moderate atherosclerosis	Atherosclerosis of coronary arterioles and mitral valves (interventricular septum and auricular walls). Myocardium without alteration	Increased	Decreased II Increased I	Decreased III from isoelectric to negative
6, M	108	494	636	721	765	198	2.233	Moderate atherosclerosis	Atherosclerosis of coronary arteries (left auricular and left ventricular walls and great vessels). Myocardium without alteration	Increased	Decreased II, III, V	No change
9, M	127	361	636	695	765	1641	10.791	Marked atherosclerosis	Atherosclerosis of coronary arteries (left ventricular wall and left anterior papillary muscle). Myocardium, focal myocarditis of the right auricle	Increased	Decreased I, II, III	Decreased V from positive to negative
10, F	112	361	833	551	507	454	7.568	Marked atherosclerosis	Atherosclerosis of coronary arteries, larger and smaller branches (left anterior papillary muscle, auricular walls, and great vessels). Myocardium, areas of swelling and vacuolar degeneration	No change	Decreased I, II, III, V	Decreased IV, V
11, F	104	399	938	1072	1210	113	15.441	Marked atherosclerosis	Atherosclerosis of coronary arteries (left anterior papillary muscle and interventricular septum). Myocardium without alteration	Decreased	Increased I, II, III	Decreased IV, V

of the aorta in the cholesterol-fed rabbits ranged from 1.217 to 15.441 Gm., with a mean of 6.701 Gm. per 100 Gm. of dry aorta (Table I).

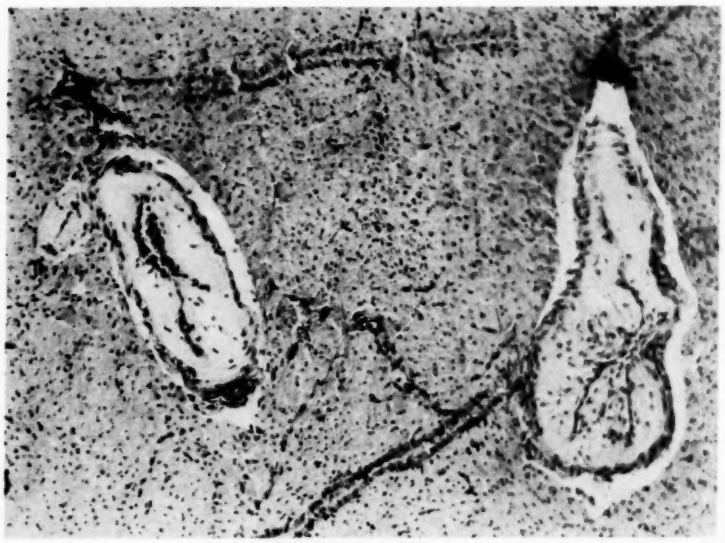

Fig. 1.—Photomicrograph of section of heart of cholesterol-fed rabbit 9, showing two markedly atherosclerotic coronary arterioles and the normal myocardium. (H&E × 170.)

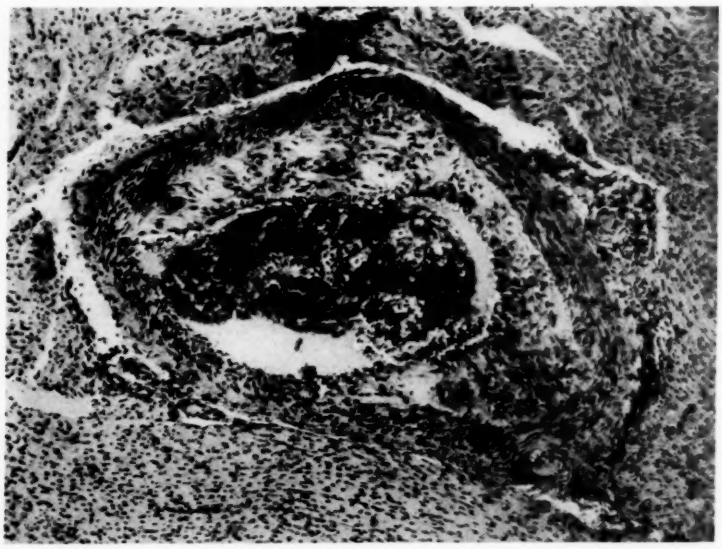

Fig. 2.—Photomicrograph of section of heart of cholesterol-fed rabbit 11, showing marked arteriosclerosis of a coronary artery. (H&E × 130.)

Pathologic Observations.—On macroscopic examination, the aortas of the control rabbits appeared normal. The degree of atherosclerosis observed macroscopically in the cholesterol-fed animals paralleled very closely the cholesterol content of the vessels. On microscopic examina-

tion, the aorta, coronary arteries, coronary arterioles, and myocardium were essentially normal in the control rabbits. In the cholesterol-fed rabbits, marked atherosclerotic intimal thickening of coronary arteries and arterioles was present in each heart. A few scattered foci of lymphocytic infiltration of the myocardium (auricular or ventricular) were noted, and there were no changes indicative of myocardial degeneration or infarction (Figs. 1 and 2, Table I).

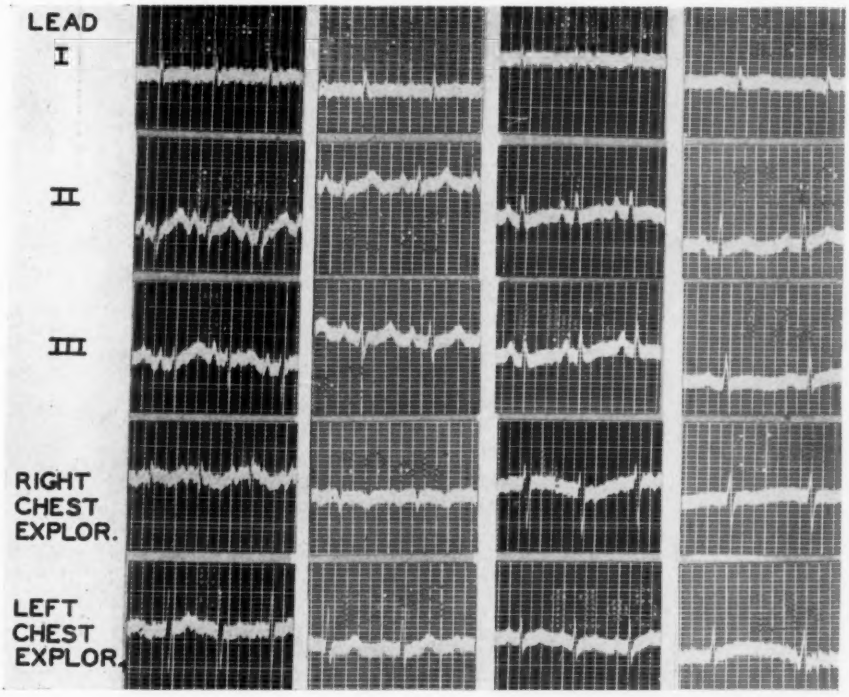

Fig. 3.—*A*, Electrocardiogram of control rabbit 12 on June 6, and *B*, electrocardiogram of same rabbit on October 11 (same year), showing only slight changes in the QRS and T waves. *C*, Electrocardiogram of cholesterol-fed rabbit 11 on June 6 prior to cholesterol feeding, and *D*, electrocardiogram of same rabbit on October 11 after four months of cholesterol feeding, showing minor changes in the QRS and T waves which are difficult to evaluate.

Electrocardiographic Studies.—No significant changes in the heart rates or in the electrical axis were observed in either the control or cholesterol-fed rabbits. The total voltage as judged by R or R plus S in Leads II and III appeared to decrease in both groups during the 126 days of observation; however, in the cholesterol-fed rabbits an increase in the voltage occurred within three to six weeks after cholesterol feeding was begun, but after this period the voltage returned rapidly to that of the control rabbits. No significant changes in the P-R or QRS intervals were observed in the experimental animals. The RS-T segment varied appreciably with the respiratory phase; however, no definite alterations were observed in the cholesterol-fed group. In

both control and experimental animals, the T waves were more subject to change in the exploratory leads than in the other leads; either no change, an increase, or a decrease characterized the unpredictable T wave direction. Extrasystoles occurred in both control and cholesterol-fed rabbits infrequently and were more often associated with slow heart rates (Fig. 3, Table I).

Levy and co-workers[4] recently reported alterations in the electrocardiograms of patients with coronary sclerosis during rebreathing of low oxygen mixtures. A control rabbit was made to breathe 10.5 per cent oxygen for twenty to thirty minutes, but only minimal electrocardiographic changes were noted as a result of this procedure. However, each of two rabbits with hypercholesterolemia induced by cholesterol feeding for a period of seven months showed a sharp decrease of the QRS voltage in Leads I, II, and III, and changes of the T wave in the exploratory leads during the administration of this low oxygen mixture.

DISCUSSION

Our results indicate that although marked narrowing occurs in coronary arteries and arterioles of rabbits fed cholesterol over a prolonged period of time, no evidence of myocardial degeneration or of significant electrocardiographic changes is observed.

In a limited study, it appears that on administration of gas mixtures low in oxygen, the nutrition of the myocardium is seriously affected in cholesterol-fed rabbits with the assumption, of course, that the electrocardiographic deviations observed are significant. These findings substantiate the conclusions of Wilson[5] that the activity of the coronary arteries themselves makes no recognizable contribution to the form of the electrocardiogram and the diseases of the arteries have no known effect upon the action currents of the heart, except so far as they temporarily or permanently alter the blood supply to some portion of the myocardium.

CONCLUSIONS

Although coronary arteries and arterioles of rabbits fed cholesterol over a prolonged period of time showed pronounced atherosclerosis, no evidence of structural change in the myocardium or of significant alterations in the electrocardiogram was observed. In a limited study it appeared that, as a result of the atherosclerotic vascular narrowing, the nutrition of the myocardium was seriously affected in cholesterol-fed rabbits, as revealed by electrocardiographic studies during the rebreathing of gas mixtures low in oxygen.

Grateful recognition is given to Marcella F. Hughes and Beatrice Tanney, B.A., for aid in taking the electrocardiograms; to Samuel Member, B.S., and Sylvia Ehrlich, B.A., for their help in the chemical studies; and to Julius Wilensky, B.S., for general assistance.

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A NEW CLAMP FOR THE GRADUAL OCCLUSION OF CORONARY ARTERIES

KENTON R. PHELPS, M.D.
CLEVELAND, OHIO

BECK and his associates in 1932 demonstrated in dogs the presence of blood vascular connections between the myocardium that had been intentionally rendered ischemic and an onlay graft of pectoral muscle.[1] Feil and Beck[2] applied this principle of collateral circulation to human patients suffering from myocardial ischemia due to coronary arteriosclerosis. Because of this work considerable impetus has been given to the study of surgical methods for augmenting the blood supply to the myocardium. The myocardial ischemia was effected in the original animal experiments by successively closing a silver U-shaped clamp at repeated operations. Since that time studies in this laboratory by Beck, Mautz and Thornton and elsewhere by others have given rise to a number of ingenious devices for effecting this coronary artery occlusion, the aim of each being gradual occlusion to simulate that occurring in coronary arteriosclerosis. The most widely used clamps operate on the principle of the screw, being fractionally closed in multiple stages at a rate found practical by experience, usually requiring three or more stages and attended by high operative mortality. To avoid the necessity of reopening the chest each time further closure was desired, Thornton and Mautz[3] in this laboratory and Blum, Schauer and Calef[4] in New York extended the screw-arm to an easily accessible subcutaneous position. All of these clamps, however, share the objectionable feature of permitting only periodic abrupt increase in closure rather than a continuously progressive closure which so often occurs in coronary arteriosclerosis.

A clamp is here described which, utilizing the principle of osmosis, effects gradual arterial closure at a fixed rate by the swelling of a contained charge of hypertonic solution. The clamp (Fig. 1*B*), constructed of pure silver, is approximately 2.5 cm. long. It is composed of a cylindrical barrel (*a*) which holds the hypertonic charge. On the anti-arterial end it is closed by a semipermeable membrane of measured porosity (*b*), held in place by a perforated screw-top (*c*), and on the other (arterial) end an L-shaped extension (*d*) holds the artery which is compressed by a piston (*e*) moved by the swelling hypertonic charge

From the Laboratory of Surgical Research, Department of Surgery, Western Reserve University School of Medicine.

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(*f*). The open limb of the L-shaped end is closed by means of an arm on a sliding cuff (*g*), thus holding the artery (*h*) in place within the clamp during occlusion. In order to prevent leakage of hypertonic charge, a thin latex rubber bag (*2*) is fitted into the clamp, as shown in Fig. 1 *C* and *D*, employing double metal washers (*1* and *3*).

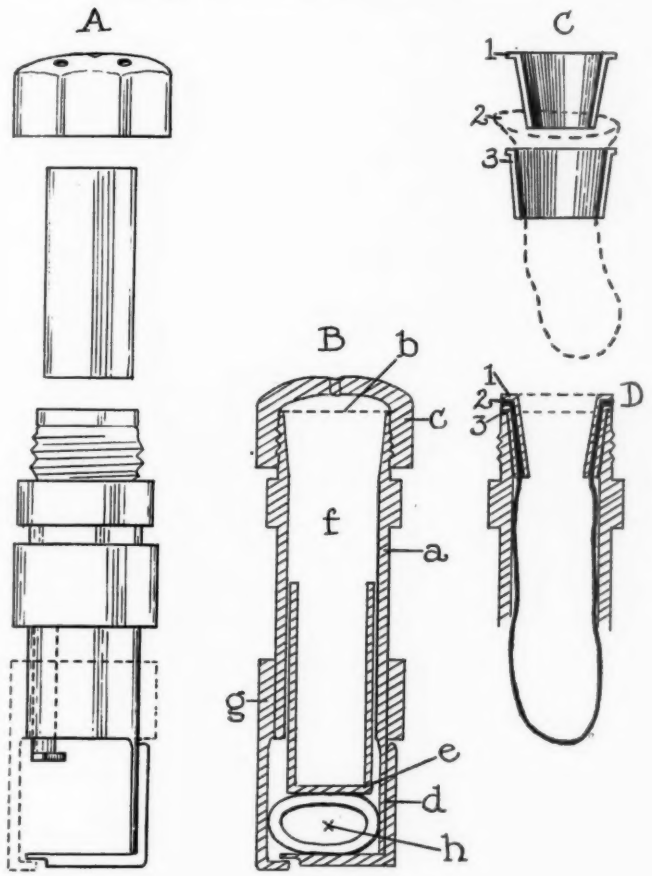

Fig. 1.

The rate of increase in volume of the hypertonic charge, and therefore the rate of closure of the clamp, is a function of two variables: (1) membrane porosity, and (2) solution (charge) concentration. The membranes used in this work are prepared after the method described by Elford,[5] yielding a tough membrane of uniform porosity. With a 100 per cent sucrose charge, membranes have been used in this work that have closure periods varying from 48 hours to 60 days. Less permeable and therefore slower closing membranes can be made but have not yet been used. The hypertonic charge employed has been 100 per cent sucrose solution, which possesses two advantages: (1) because

of high viscosity the possibility of pressure leaks within the clamp is minimized, and (2) the osmotic pressure developed is high.

Arterial closure with this clamp is done most advantageously because: (1) Only one surgical procedure is required; (2) arterial constriction progresses at a constant rate, though slowing up terminally because of charge dilution; (3) any desired rates of closure within wide limits can be provided by control of membrane porosity and charge concentration. The results of the use of this clamp will be presented in a later publication. We have used it in obtaining satisfactory gradual closure of the coronary arteries, the abdominal and thoracic aortae, and the pulmonary and renal arteries. It is suggested that this clamp will find use in the study of occlusion effects of other arteries. Clinically it might be employed to occlude large arteries slowly when acute occlusion is hazardous.

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Department of Clinical Reports

A CASE OF BACTERIAL ENDOCARDITIS ILLUSTRATING THE MECHANISM OF LOCALIZATION AND THE NATURE OF VEGETATIONS

ARTHUR C. ALLEN,* M.D.
NEW YORK, N. Y.

IN A recent paper[1] the general principles of a concept of the mechanism of the localization of vegetations were outlined. Briefly, this concept is based on laws of hydrodynamics and states, in effect, that vegetations occur primarily at sites which are selectively subjected to the greatest impact of, and contact with, the blood stream, and, thereby, with the bacteria and bacterial products circulating within that blood stream. Accordingly, stenotic and insufficient valves, particularly at their distal edges, are common sites of localization. On the basis of this concept, the attempt was made to account for the fact that vegetations are found with great frequency (1) on rheumatic, fibroplastically deformed valves, (2) on the left side of the heart, and (3) at sites of congenital malformations. It was pointed out further that the organisms which cause acute bacterial endocarditis manifest a greater predilection for the right side of the heart than do those responsible for subacute bacterial endocarditis. This fact dovetails with the concept on the theoretical ground that the virulent organisms which give rise to acute endocarditis, e.g., the *Streptococcus hemolyticus,* gonococcus, etc., require the advantages of "impact and contact" to a lesser extent because of that virulence. These conceptions are obviously directly opposed to the theories that the localization of vegetations is determined by bacterial embolism through the medium of the coronary arteries, by impingement of the cusps against each other at the line of closure, or by eddy currents.

At the time of the original communication it was realized that many odd sites of localization of vegetations are encountered, principally because of cardiac anomalies, but also as a result of distortions caused usually by previous rheumatic involvement or, rarely, by foci of healed myomalacia (e.g., with perforation of the interventricular septum). To render a theory of localization tenable, it is obviously mandatory that the same general principles be applicable to each case, notwithstanding marked differences in the underlying physical conditions. The following case illustrates this point.

CASE REPORT

History.—S. S. (445775). The patient was a 15-year-old white schoolgirl with a history of "heart disease," diagnosed at the age of 7 years. There had been

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*George Blumenthal, Jr., Fellow in Pathology.

no restriction of activity, however. Three weeks before admission she experienced chills, fever, marked weakness, and slight cough with bloodtinged sputum. A week later a course of sulfapyridine was started, but it was discontinued because of hematuria.

Physical Examination.—The temperature was 102.4° F.; the pulse rate, 86; and the respiratory rate, 20. The patient was well developed, pale, and slightly dyspneic. There were several petechiae on the soft palate. There was no clubbing of the fingers or toes. The arteries of the neck pulsated prominently, and the cervical veins were distended. The heart was enlarged both to the right and left. The apical impulse was diffusely palpable in the region of the sixth left intercostal space in the anterior axillary line. There was a coarse systolic and diastolic thrill, most pronounced in the second interspace near the sternum, which was transmitted to the left and downward, as well as upward for a slight distance. There was a loud, roaring, to-and-fro, almost continuous murmur, with a systolic accentuation, in the same areas. The heart sounds were completely obscured by this murmur except at the apex, where the second sound was loud and snapping. There was some question of an independent diastolic component at the aortic area to the left of the sternum. The pulse was of the Corrigan type, with a loud pistol shot and a Duroziez sign. The blood pressure was 130/20. There was a marked capillary pulsation. The tip of the spleen was felt about 2 cm. below the costal margin. The liver was not palpable.

Laboratory Data.—The hemoglobin was 73 per cent; the erythrocyte count, 3,730,000; and the leucocyte count, 6,800; the differential count was normal. The urine contained albumin (+++) and a few erythrocytes and leucocytes. The blood Wassermann reaction was negative. The blood urea nitrogen was 12 mg. per cent. Blood culture revealed sixty colonies of *Streptococcus viridans* per cubic centimeter. A roentgenogram of the chest showed a marked widening of the contour of the heart which was suggestive of pericardial effusion. The electrocardiogram revealed sinus tachycardia; the P-R interval was 0.2 second; the QRS wave was slightly slurred and measured 0.1 second. The electrocardiogram was interpreted as indicating myocardial disease. A phonocardiogram demonstrated a high-pitched murmur which was present throughout systole and continued, at least in certain areas, into diastole. Also, a diastolic, high-pitched murmur was recorded over the mesocardium and the pulmonic area.

Course.—The patient received 1 Gm. of sulfanilamide every four hours for seven days (total dose, 41 Gm.). Nevertheless, she continued to have a fever which ranged from about 100° to 104° F. Eleven days after admission the patient was transfused, and she died several hours later.

Clinical Diagnosis.—The possibilities considered were patency of the ductus arteriosus with patency of the interventricular septum, or an aortic lesion, or both, and subacute bacterial endocarditis.

Autopsy.—The autopsy was performed four hours after death. The body was that of a well-developed, but poorly nourished, 15-year-old white girl, with marked pallor of the skin and mucous membranes. There was no clubbing of the fingers or toes. There was a bilateral pleural effusion (750 c.c. on the right and about 500 c.c. on the left). The spleen was enlarged; it extended 5 cm. below the costal margin in the left anterior axillary line.

Heart.—The heart was distinctly enlarged and weighed 575 Gm. There were about 40 c.c. of clear, light-yellow fluid within the pericardial sac. The epicardial surface was smooth and glistening except for several small, gray-white, firm flecks on the posterior aspect of the right auricle. This chamber was not dilated or hypertrophied. The foramen ovale was closed. The opening of the coronary sinus was in its normal position. The ring of the tricuspid valve measured 11 cm. in circumference. The cusps were not thickened, and the chordae tendineae were thin and inserted in a weblike manner. The right ventricle was moderately dilated and

hypertrophied. The wall measured 6 mm. in thickness at a distance of 2.5 cm. from its base. The ring of the pulmonic valve measured 76 mm. in circumference. The cusps were slightly thickened at their distal edge, but were pliable, and there was no stenosis. At the bases of the cusps there were clusters of finely granular, friable, tawny vegetations which averaged 1 to 2 mm. in height. Directly below the anteroposterior commissure there was an oval, obliquely placed interventricular septal defect which measured 1.5 by 1.2 cm. Protruding through this defect, and occluding about nine-tenths of it, was the folded right cusp of the aortic valve

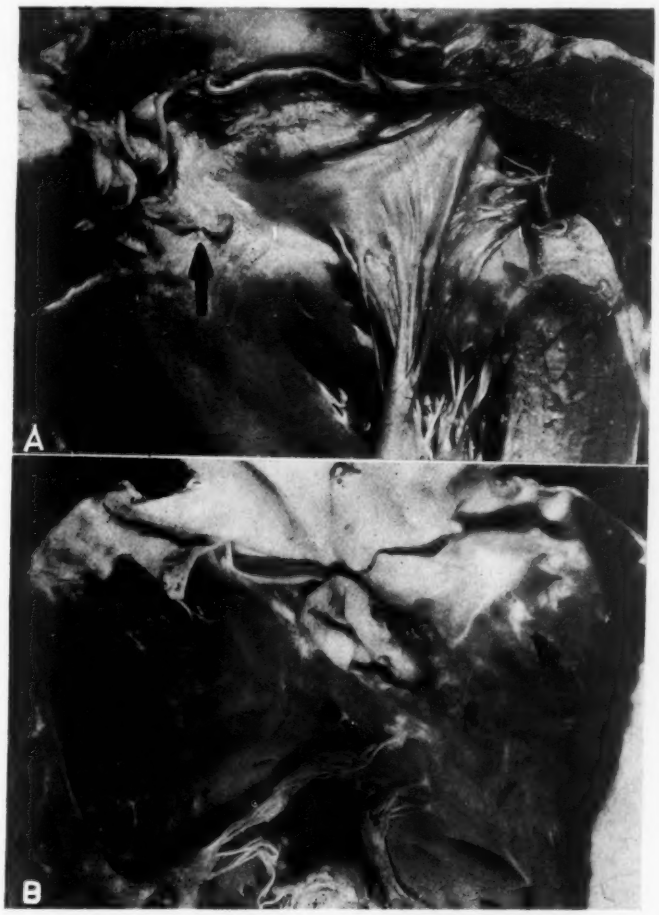

Fig. 1.—*A*, Left ventricle. Note regurgitation pockets, with small vegetations on superior aspect. Note also vegetations at base of posterior aortic cusp. *B*, Right ventricle. Observe the interventricular septal defect, with eventrated right aortic cusp anchored to anterior pulmonic cusp. The vegetations partially rim the defect and involve the aortic and bases of the pulmonic cusps. The free edges of the cusps are spared, as is the mural endocardium opposite the septal defect. Note the "stenotic" endocardial pockets (arrow).

(Fig. 1). This position of the aortic cusp must have been constant, because it was firmly anchored near its base by fusion with the anterior pulmonic cusp. The septal defect was rimmed over approximately two-thirds of its circumference by finely granular, small vegetations which were also present on the lateral aspect of that portion of the aortic cusp which protruded into the right ventricle. A Gram stain of the crushings of these vegetations revealed numerous Gram-positive cocci in pairs

and short chains. *Streptococcus viridans* was obtained from a culture of the vegetations. Smoother, dew-drop vegetations, 1 to 2 mm. in height, were located in the mural endocardium directly along the outflow tract of the right ventricle. The subvalvular endocardium was thickened and gray-white. There were, in addition, endocardial pockets which faced in a direction opposite that of the pulmonic valve (Fig. 1*B*). There were no vegetations in these pockets.

The left auricle was slightly dilated and hypertrophied. There was moderate wrinkling and thickening of the endocardium of the posterior wall of the auricle. The ring of the mitral valve measured 10 cm. in circumference. There was minimal thickening of the free edge of the valve at the junction of the anterior and posterior cusps. However, the chordae tendineae were thin and were inserted into the substance of the valve in the normal fanlike fashion. The left ventricle was distinctly dilated and hypertrophied. Its cavity measured 11 by 12.5 cm., and its wall was 24 mm. thick at a distance of 4.5 cm. from the base. The papillary muscles were hypertrophied. The myocardium was of a homogeneous, purple-brown color, except in the subendocardial zones of the papillary muscles, where it was yellowish tan. The aortic ring measured 65 mm. in circumference. The posterior cusp was large; it measured fully 24 mm. in breadth. Its free edge was rolled, but its commissures were not fused. There was a slight, glistening nodularity of the ventricular aspect of the cusp. In the right lateral portion of the base of the cusp there was an irregular 3 by 3 mm. vegetation. The right and left cusps were fused, although a distinct raphe persisted between them. Almost the entire right aortic cusp, which was diffusely thickened to a slight degree, was folded into the interventricular defect in such a way that the resistance offered by this cusp to the column of blood returning in diastole must have been negligible. In consequence, there was a distinct aortic insufficiency. The point of major interest lay in the endocardial ridges and regurgitation pockets, which were approximately 22 mm. and 26 mm. below the level of the free edge of the aortic valve (Fig. 1*A*). They were at the site where the blood returning in diastole through the insufficient valve would impinge on the mural endocardium. The small insufficiency pockets faced, in characteristic fashion, in the same direction as the normal aortic cusps, and in a direction opposite that of the endocardial pockets caused by stenosis, such as those which were found in the right ventricle (Fig. 1). These pseudo valves were covered at their free edges and in their depths with fine, granular, tawny vegetations. Other small regurgitation pockets were present near the posterior papillary muscles. These, too, lay in the path of the diastolic backflow. One of the endocardial ridges referred to above was slightly undermined in a direction facing the apex of the heart. There were no vegetations at either of these sites.

The coronary ostia were widely patent, and the vessels showed a minimal degree of sclerotic narrowing.

There were no pertinent changes in the remaining organs. Permission to examine the brain was not obtained.

Microscopic Observations.—Sections through the insufficiency pockets revealed the presence of the characteristic vegetations of bacterial endocarditis, superimposed on a fibrous projection of mural endocardium. The bulk of the reaction was localized to the superior, free edge of the pockets. The bases of these vegetations were composed of a vascular, apparently recently formed, cellular granulation tissue, in which the principal cell was a large, vesicular histiocyte. These histiocytes exhibited a slight tendency toward vertical arrangement and palisading. Van Gieson's stain and Mallory's aniline blue stain showed that the fibrous tissue of the underlying regurgitation pockets frayed out and merged with the granular, fibrinoid material which composed the periphery of the lesion. In some portions of the periphery the collagenous fibers were disrupted into small, granular fragments which extended to the very edge of the vegetation. One frequently saw nonnucleated fibers of col-

lagenous tissue fanning out from the fibrous pseudo valve toward the fibrinoid periphery. These fibers manifested a progressive loss of affinity for the acid fuchsin of the van Gieson stain until, near the edge of the lesions, they stained yellow and resembled strands of fibrin (Figs. 2 and 3).

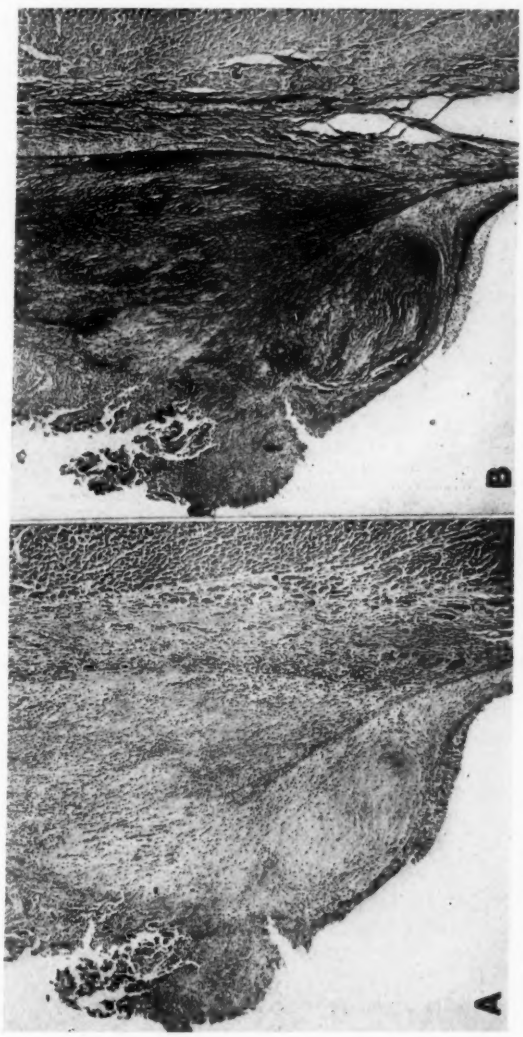

Fig. 2.—Contrast sections of regurgitation pocket stained with H & E (*A*) and Weigert's elastic tissue and van Gieson's stain (*B*). Note that the vegetation, which closely resembles a simple thrombotic deposit in *A*, is found really to contain isolated fragments of disrupted, nonreparative, collagenous tissue (*1*). Note the frayed collagenous fibers at the base of, and within, the vegetation (*2*).

A section through the anterior cusp of the pulmonic valve revealed evidence, in the form of proliferation, palisading and vertical arrangement of basophilic histiocytes, hypercapillarization, and eosinophilic degeneration of the elastic and collagenous tissue, of acute rheumatic inflammation. The cellular infiltration was found on both the ventricular and arterial aspects of the valve. At its base there was a vegetation characteristic of bacterial endocarditis. More distally, along the ventricularis, there were minimal, superficial foci of bacterial endocarditis. A section through the vegetations on the posterior aortic cusp presented a similar picture of acute rheumatic endocarditis, combined with bacterial inflammation.

Sections of the myocardium revealed scattered Aschoff bodies. There was also slight myofibrosis, which was principally perivascular in distribution.

The histologic changes in the remaining organs were not significant; the focal renal glomerular lesions which are characteristic of subacute bacterial endocarditis were absent.

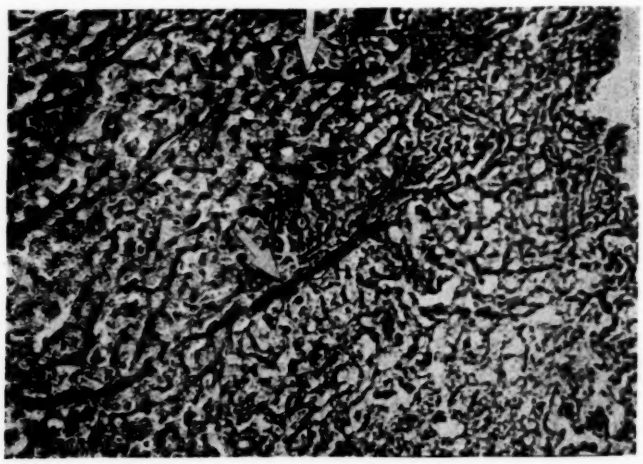

Fig. 3.—High-power magnification of portion of Fig. 2*B*. Note the collagenous fibers (arrows) merging with the fibrinoid, necrotic tissue. If these few remaining fibers had been destroyed, as not infrequently happens, the vegetations would be almost indistinguishable from a simple thrombotic deposit.

Anatomic Diagnoses.—

1. Congenital heart disease
   a. Patency of membranous portion of interventricular septum.
   b. Eventration of right aortic cusp into septal defect and fusion of it with anterior pulmonic cusp.
   c. Aortic insufficiency and pulmonic stenosis.
   d. Moderate dilatation and hypertrophy of both ventricles.
2. Rheumatic heart disease
   a. Acute rheumatic aortic and pulmonic valvulitis.
   b. Acute rheumatic myocarditis.
3. Bacterial endocarditis (*Streptococcus viridans*) involving:
   a. Margin of ostium of septal defect in right ventricle.
   b. Mural endocardium of right ventricle.
   c. Endocardial regurgitation pockets in left ventricle.
   d. Posterior and right aortic cusps.
   e. Pulmonic valve.
4. Pulmonary edema and congestion.
5. Bilateral hydrothorax.

DISCUSSION

The physical conditions in this case were as follows: The base of the right aortic cusp was firmly adherent to the anterior pulmonic cusp. This anchorage, which was apparently congenital, was made possible by the patency of the membranous portion of the interventricular septum. As a result, most of this aortic cusp lay within the septal defect and practically occluded it, although there appeared to be sufficient residual patency to account in part for the systolic thrill and murmur.

In addition, a portion of this same cusp actually projected into the right ventricle, with the result that a stenosis was produced. This stenosis was more likely the major cause of the systolic thrill and murmur. There was striking indirect evidence of the existence of a stenosis, namely, the presence of subvalvular endocardial pockets which faced in a direction opposite that of the pulmonic valve, and a diffuse, subvalvular, endocardial sclerosis (Fig. 1*B*). Inasmuch as the pulmonic cusps could not have produced the stenosis, the protruding, fixed aortic cusp must have been responsible for it. In other words, the level of the narrowed orifice was not at the free edge of the valve, as it is in ordinary cases of rheumatic pulmonic stenosis, but rather at the site of protrusion of the eventrated aortic cusp and at the bases of the pulmonic cusps, which were approximately on the same plane. Furthermore—and this is the point to be emphasized—the vegetations were located, not at the line of closure of the valve, where they are ordinarily situated, but at the level of the stenosis. In this case, the level of stenosis was below the distal edge of the cusps because an anomalous, protruding aortic cusp encroached on the pulmonary outlet. *This is the site which suffered the greatest impact of, and contact with, the blood stream* because of the accelerated velocity of ejection, frictional resistance, and exposure to a greater surface area of blood, and, therefore, to a greater number of bacteria, as well as to other hemodynamic factors which are discussed in more detail elsewhere.[1]

The presence of a minute, superficial lesion of bacterial endocarditis near the mid-portion of the ventricular aspect of the pulmonic and aortic cusps, and the characteristic absence of involvement of the arterial surface are regarded as direct consequences of the fact that a greater quantity of blood, and of bacteria, brushed by the ventricularis than by the opposite surface during each cardiac cycle. This selective localization occurred in spite of the acute rheumatic involvement of both aspects of the cusps. Stated in another way, the entire ventricular surface of the semilunar valves suffered the hemodynamic disadvantage of selective "contact," which, in this case, was enhanced at the base of the pulmonic valve by the presence of stenosis at this level.

Small mural vegetations were also found directly along the outflow tract of the right ventricle, where the effects of the stenosis were, of course, felt, albeit to a lesser degree.

The left ventricle presented an even more striking demonstration of the dominant role which the factors of impact and contact play in the selective localization of vegetations. Because of the eventration of the right aortic cusp, there was a marked incompetence of the aortic valve; this was localized to the site normally occupied by this cusp. This leak was apparently the cause of the diastolic murmur. Immediately below this site there was striking evidence, in the form of endocardial pockets which faced in the same direction as normal aortic valves (Fig. 1*A*), of

the insufficiency. Shallow endocardial pockets or curved endocardial ridges are sometimes referred to as Zahn's[3] valves, and the larger, deeper, horseshoe-shaped pockets as Schmincke's[4] valves. It is relevant to mention briefly the theories of the pathogenesis of these endocardial pockets. These include the (1) mechanical (constant impingement of a regurgitant stream of blood), (2) congenital, and (3) inflammatory (Ribbert[5]). It is important to be reasonably certain that the formation of the endocardial pockets in this case preceded the bacterial endocarditis. However, the bacterial endocarditis could hardly have led to the formation of these pseudo valves, for parts of the immediately adjacent endocardial ridges and pockets were composed of old fibrous tissue which was entirely free of endocarditis. Exclusion of the possibility that the pockets were congenital is made difficult by the fact that there were coexistent cardiac anomalies. However, in the presence of frank aortic insufficiency, these pockets were more likely caused by the continual impact of the regurgitant stream against the mural endocardium.

It is clear, then, that these endocardial outpouchings suffer, to a selectively increased degree, the brunt of impact by the diastolic stream as it returns through the insufficient valve and is reflected from this part of the wall. This repeated pounding leads to local fibrous tissue thickening of the endocardium, and this is molded by the jet into a shallow pocket. It was, therefore, not surprising, but rather in conformity with the principles of the concept, to find vegetations localized to these endocardial pockets to the exclusion of other portions of the mural endocardium of this chamber. Still more graphic confirmation was afforded by the histologic observation that the vegetation was practically confined to the depth and free edge of the pocket, where the direct impact of, and contact with, the diastolic backflow would be greatest, whereas the more protected undersurface was essentially spared (Fig. 2). It is interesting, also, that the vegetation was located at the base of the posterior aortic cusp, in direct line with the diastolic stream.

Nature of the Vegetations.—Another point of major interest lies in the nature of these vegetations. The histologic evidence bears out the conclusion reached elsewhere (Allen[2]) that the vegetations of bacterial endocarditis are not thrombi deposited from the blood on an inflamed endocardial surface, but are really derived from necrotic valvular tissue, forced apart by the plasma and blood elements which are exuded from the eroded or abnormally permeable valvular blood vessels that are part and parcel of inflamed valves. In this connection, one is reminded of the remarkable frequency with which atheromatous "ulcers," with no overlying endothelium, occur in the aorta *without superimposed thrombi.* It is, of course, maintained that the bacteria are implanted upon the valves from the blood within the chambers in the vast majority of instances.

SUMMARY AND CONCLUSIONS

1. A case of bacterial endocarditis caused by *Streptococcus viridans*, in a heart with a large interventricular defect through which an aortic cusp had eventrated, with resulting pulmonic stenosis and aortic insufficiency, is reported.

2. The vegetations were localized to regurgitation pockets in the mural endocardium of the left ventricle, where there was constant impact by the regurgitant stream as a result of the aortic insufficiency.

3. The localization of vegetations at sites which are subjected to various hemodynamic forces is explained as the result of impact of, and contact with, the blood stream, and with bacteria circulating therein.

4. The histologic observations confirmed the concept previously advanced, namely that the vegetations of bacterial endocarditis are derived from necrotic valvular tissue, and the plasma and blood elements from eroded valvular blood vessels; this occurs after implantation of bacteria from blood within the chamber. This is contrary to the current concept that the vegetations are thrombi which are deposited on an inflamed endocardial surface as the blood flows past the valves.

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Department of Reviews and Abstracts

Selected Abstracts

Asmussen, Erling, and Chiodi, Hugo: The Effect of Hypoxemia on Ventilation and Circulation in Man. Am. J. Physiol. **132:** 426, 1941.

Respiration.—Experiments have shown that hypoxemia caused by partial CO poisoning (20 to 30 per cent) (anemic hypoxemia) elicits little or no respiratory response whereas hypoxemia caused by an alveolar pO_2 of about 40 mm. Hg (hypoxic hypoxemia) causes a very pronounced hyperventilation in both rest and work.

It is concluded: 1. General O_2 deficiency in the tissues does not evoke a hyperventilation. 2. The O_2 *tension* of the arterial blood, and not its O_2 *content*, is the active factor in causing hyperventilation. 3. The effect is produced through the pO_2 of the carotid body (glomus).

Circulation.—Experiments have shown that both in rest and during work a state of ***hypoxic hypoxemia***, with the O_2 in the inspired air low enough to reduce the arterial HbO_2 to 70 or 80 per cent, produces an increase in cardiac output above the normal. Furthermore, both in rest and during work a state of *anemic hypoxemia* (20 to 30 per cent Hb saturated with CO) has little or no effect on cardiac output, but increases the pulse rate considerably.

It is concluded: 1. Acute O_2 deficiency in the tissues is not a stimulus for the circulation. 2. A lowered O_2 *tension* of the arterial blood, not a lowered O_2 *content*, is a stimulus for the circulation. 3. The effect probably is produced through the chemoreceptors of the carotid glomus.

AUTHORS.

Mangun, George H., Reichle, Herbert S., and Myers, Victor C.: Further Studies on Human Cardiac and Voluntary Muscle. Possible Implications of Changes in the Creatine, Phosphorus, and Potassium Content, With Special Reference to Heart Disease. Arch. Int. Med. **67:** 320, 1941.

Creatine, phosphorus, and potassium determinations have been carried out on samples of muscle from the left and right ventricles of hearts obtained at autopsy from human beings with pathologic conditions. In forty-eight instances analyses were also carried out on voluntary muscle.

The content of creatine, phosphorus, and potassium in the left and right ventricles and in voluntary muscle averaged about 5 per cent less than in samples from thirteen normal persons and varied considerably more.

In seventeen patients with congestive heart failure, the creatine, phosphorus, and potassium concentrations of both ventricles and of voluntary muscle were consistently decreased. The percentage decrease was greatest for creatine and least for phosphorus, while potassium occupied an intermediate position.

The average figures obtained for persons with heart failure showed a loss of 4.0 mols of creatine, 6.0 mols of phosphorus, and 9.4 mols of potassium per kilogram. It is suggested that this loss is due primarily to a breakdown of dipotassium phosphocreatine with a subsequent loss of its components.

In uremia the creatine, phosphorus, and potassium contents of voluntary muscle were found to be somewhere higher than the average values, 50 per cent of the

values being higher than the normal range. Values for cardiac muscle were also relatively high. The increase in the creatine content of voluntary and cardiac muscle in uremia finds probable explanation in the retention of creatinine and the equilibrium which exists between creatinine and creatine. The changes in the phosphorus and potassium are probably related to the creatine changes.

The creatine, phosphorus, and potassium values tended to be decreased in voluntary muscle in all conditions not associated with nitrogen retention, with the possible exception of fever and emaciation. Values in cardiac muscle, on the contrary, were usually normal or slightly elevated, unless heart disease was evident.

AUTHORS.

Landt, Harry, and Benjamin, Julien E.: Changes in the Content of Carbon Dioxide in Venous Blood During Rebreathing Experiments. Comparison of Change in Persons With a Normal Heart and in Patients With Cardiac Disease. Arch. Int. Med. **67:** 72, 1941.

When subjected to rebreathing experiments, patients with cardiac disease lose carbon dioxide from the blood stream. Normal persons either maintain the carbon dioxide content or gain when subjected to like conditions. The loss of carbon dioxide from the blood stream of the patient with cardiac disease allows for a relatively greater oxygen-carrying power in the blood.

AUTHORS.

Sussman, Ralph M., and Lieberson, Abraham: Chest Lead Changes as the Sole Electrocardiographic Evidence of Heart Disease. Brit. Heart J. 3: 13, 1941.

Four thousand four-lead electrocardiograms (3,200 cases) were reviewed to assess the diagnostic value of an abnormal precordial lead when the standard leads were normal. The criteria adhered to as a basis for this selection were an absent R wave, an R wave of less than 2 mm., a QRS wave of M or W configuration, or an inverted T wave, these being found in the fourth lead, in the presence of standard leads that were without significant alterations. Of the 3,200 cases, seventy showed positive precordial and negative standard leads. Of these seventy, a characteristic group of twenty-three was completely analyzed as representative of the larger group. By careful history, physical examination, and x-ray the twenty-three cases with positive chest leads were divided into a cardiac group (57 per cent) and a noncardiac group (43 per cent). Left axis deviation occurred with about equal frequency in both groups. Coronary thrombosis was present in only one patient (8 per cent) of the cardiac group. Pulmonary disease contributed the great number of cases to the noncardiac group (four of ten). Absence of the initial upward deflection (R wave) in Lead IV was the most common finding in the cardiac group (five of thirteen cases). Low R waves occurred with about equal frequency in both groups. Inverted or biphasic T waves were present slightly more often in the noncardiac than in the cardiac group. The female sex was predominant in the ratio of about 3 to 1 in both groups.

Where the standard leads were normal, the precordial lead was the sole electrocardiographic indicator of heart disease in 1 to 2 per cent of 3,200 cases studied. An abnormal fourth lead in the presence of normal standard leads is indicative of heart disease in more than 50 per cent of such cases.

An absent R wave is of greater significance as a sign of myocardial damage than are either low R waves or inverted T waves, alone or combined.

The precordial lead may be the only electrocardiographic evidence of heart disease in conditions other than coronary thrombosis or sclerosis.

AUTHORS.

Schnur, Sidney: T-Wave Inversion, Heart Size, and Functional Capacity. Brit. Heart J. 3: 30, 1941.

The electrocardiogram, functional capacity, and cardiac size were correlated in a study of 100 consecutive patients with hypertension. There is a positive correlation between the size of the heart and functional capacity.

As the heart enlarges in hypertension, the T wave progressively becomes inverted in Leads I and II and upright in Lead III. The RS-T segment follows the T wave in its direction.

Left ventricular preponderance is a characteristic electrocardiographic pattern occurring in 35 per cent of patients with enlarged left ventricles. It occurs with increasing frequency as the heart enlarges and is characterized by (1) left axis deviation, (2) inversion of T_1 or of T_1 and T_2 with T_3 upright, and (3) a depressed RS-T segment in Lead I or in Leads I and II and an elevated RS-T segment in Lead III.

Since functional capacity and cardiac size are both directly related to left ventricular preponderance, one may estimate, with some degree of accuracy in many cases, the functional capacity and approximate size from the electrocardiographic picture.

Because depressed RS-T segments in Leads I and II and elevated RS-T in Lead III are found in 35 per cent of enlarged hypertensive hearts, and this deviation is one of the cardinal patterns of posterior coronary occlusion, one should be extremely careful in making the latter diagnosis on the cardiographic evidence alone. The origin of the RS-T take-off and the presence of Q waves are of value in the differential diagnosis.

Hypertension is the most frequent etiological cause of left ventricular preponderance. Syphilis is the next most common etiological factor.

There is no positive correlation between the level of the blood pressure and these changes. The data do not solve the problem of whether the duration of hypertension, enlargement, per se, or some other factor associated with enlargement is responsible for the T and RS-T changes.

It is not believed that the few cases of coronary occlusion or overdigitalization in the series affect the general conclusions.

AUTHOR.

Eliaser, Maurice, Jr., and Kondo, Benjamin O.: The Electrocardiogram in Later Life. Arch. Int. Med. 67: 637, 1941.

A group of 100 active, employable, asymptomatic persons between the ages of 70 and 92 years, who presented no clinical evidence of cardiac disease other than systolic mitral murmurs of the arteriosclerotic type and slow, untreated auricular fibrillation, were examined electrocardiographically.

Certain electrocardiograms which are usually considered pathologic occurred with sufficient frequency to be considered normal for this age group. They included records of left axis deviation, abnormally low voltage, sinus bradycardia, partial latent auriculoventricular conduction defects, intraventricular conduction defects, and inversion and flattening of the T waves in any or all leads.

Some changes occurred in a sufficiently small percentage of persons to warrant the impression that, when noted, they could be considered only presumptive evidence of myocardial disease. These were auricular fibrillation, bundle branch block, elevation of the ST intervals above the base line, especially in the first standard lead, and the occurrence of the type of QT changes in Lead I associated with anterior coronary occlusion.

Definite abnormalities of the cardiovascular system were suggested by electrocardiographic changes in which a prominent Q wave was observed in association with an inversion of the T wave in Lead IV F, complete auriculoventricular dissociation, and right axis deviation.

It is intimated that greater care must be taken in the interpretation of the electrocardiograms of persons in later life than in the interpretation of those of the younger age groups if errors of commission are to be avoided in the diagnosis of acute lesions of the coronary arteries.

AUTHORS.

Hamilton, F. Carlyle: The Significance of Gallop Rhythm. Canad. M. A. J. **44**: 260, 1941.

Gallop rhythm is a fairly common and easily recognizable sign of serious heart disease. It must not be confused with the rhythm created by a third physiologic heart sound.

Gallop rhythm occurs chiefly in connection with long-standing hypertension. It is always associated with serious heart disease.

The three types of diastolic gallop occur with equal frequency. The protodiastolic type has the most serious outlook.

Some evidence is presented to suggest that the prognosis is most serious when gallop rhythm occurs during the fourth decade of life, since many of these cases result from hypertension secondary to chronic nephritis or from malignant hypertension.

In older patients with gallop rhythm the immediate prognosis was found to be somewhat better than anticipated; this should encourage us to treat thoroughly the underlying heart condition in all such cases.

AUTHOR.

Scherf, David: An Experimental Study of Reciprocating Rhythm. Arch. Int. Med. **67**: 372, 1941.

An auriculoventricular rhythm was produced in dogs' hearts in situ; functional longitudinal dissociation appeared after the conduction system was fatigued by means of a series of extrasystoles or during stimulation of a vagus nerve. In this stage return extrasystoles (reciprocating beats) appeared whenever the R-P interval of the auriculoventricular beats was prolonged. The experiments prove that under certain conditions bigeminal or trigeminal rhythm may be due to a re-entry mechanism.

AUTHOR.

Stewart, Harold J., and Bailey, Robert L., Jr.: The Cardiac Output and Other Measurements of the Circulation in Coarctation of the Aorta. J. Clin. Investigation **20**: 145, 1941.

This study concerns fourteen cases of coarctation of the aorta. The diagnosis was made during life in thirteen of these and at autopsy in one case; in four cases it was confirmed by autopsy in patients who died some time after the diagnosis had been made.

The following observations were made in nine of these cases: cardiac output, basal metabolic rate, arteriovenous oxygen difference, cardiac output per beat, left ventricular work per beat, the blood pressure in all four extremities, venous pressure, vital capacity, circulation time by means of decholin, carbon dioxide inhalation,

and mascosol, electrocardiograms, and x-rays of the chest. Clinical observations of five other patients are included in Table I.

The heart at rest was found to maintain a normal or even increased volume output of blood in coarctation of the aorta before the onset of failure. In only one of the nine cases was the cardiac output decreased. In only one of these patients was the heart enlarged to give a cardiothoracic ration greater than 50 per cent. The work of the heart in relation to the cardiac size was, as a consequence, adequate in all except this one case. This patient had a cardiac output within normal limits, but it was not in proportion to the greatly enlarged heart.

The systolic blood pressure in the arms was higher than that in the legs in all except one patient. This finding was the most constant of the characteristic signs of coarctation of the aorta. In most cases, there was not only an increase in the resistance to the outflow of blood at the site of coarctation and in the collateral channels, but also a generalized increase in peripheral resistance sufficient to maintain a high diastolic pressure below the level of the coarctation.

The circulation time was within or near normal limits above the level of coarctation, but there was a tendency to prolongation below the coarctation.

Erosion of the inferior margins of the ribs posteriorly, giving rise to scalloping and notching, was the most common x-ray finding in coarctation of the aorta. This was noted in eleven of the fourteen cases.

Enlargement of the heart and T-wave changes in the electrocardiogram point to poor prognosis when they occur.

AUTHORS.

Bedford, E. Evan, Papp, Cornelio, and Parkinson, John: Atrial Septal Defect. Brit. Heart J. 3: 37, 1941.

A patent foramen ovale (patent to probe or even to pencil), found in 20 to 30 per cent of all necropsies, is an anatomic variation of a normal condition; it is clinically silent except that, when it is distended by increased right auricular pressure ("widely patent"), it can give rise to terminal cyanosis and paradoxical embolism. In contrast, atrial septal defect (A.S.D.) is a real congenital malformation due to a defective union or malformation of the three embryonic septa forming the definitive atrial septum. It occurs (a) as a single lesion and constitutes 7 to 25 per cent of all congenital heart lesions, (b) as an associated lesion with any other congenital heart lesion, and (c) combined with mitral stenosis, and then probably with auricular fibrillation.

A diagnosis of A.S.D. was made in fifty-three patients, ten with necropsy control and forty-three without. An association with mitral stenosis was present in four of the necropsy cases (one also had adhesive pericarditis), in four of the clinical cases, and with patent ductus arteriosus and ventricular septum defect in one necropsy case. The lesion may be found at any age, and the prevalence of females was striking (4:1). The age of death was mostly between 30 and 50. The cause of death was congestive heart failure in three, pulmonary infarction in two, embolism (one paradoxical) in two, subacute bacterial endocarditis in one, bronchopneumonia in one, and operation in one.

The pathologic findings in the ten necropsy cases were:

(a) A large heart consisting mainly of right ventricle, conus, and right auricle, with a disproportion between right and left cavities of about 3:1 in bulk, or even more in cases of associated mitral stenosis.

(b) Gross dilatation of the pulmonary artery and its branches, except in one case where there was a big conus with a normal pulmonary artery. Severe arteriosclerosis (with thrombosis of the pulmonary artery and branches) was found only once, and in lesser degree three times; the remainder showed simple thickening only.

(c) The atrial septum was almost absent in one; the defect involved the lower part of the septum, and there was an imperfect formation of the tricuspid valve (persistent ostium primum) in another; and its site was the enlarged fossa ovalis or the upper part of the septum in the remainder. The dimension of the defect varied from 1 by 0.8 cm. to 7 by 4 cm. There was no strict relation between the dimension of the defect and the degree of pathologic adjustment.

Auditory signs in A.S.D. are lacking, for the lesion itself produces no murmur. Any murmurs heard are due to dilatation of the right ventricle and the conus, and relative stenosis of the less distensible pulmonary ring. A systolic murmur in the pulmonary area was found in thirty-two and was accompanied by a systolic thrill in thirteen cases. An accentuated pulmonary second sound in thirty-one was followed by a diastolic murmur in ten; no murmurs were recorded in eight cases. A forcible and displaced apex beat without other cause and due to the large right ventricle proved to be a most suggestive sign (thirty-two cases). Common clinical features in our fifty-three cases were fair capacity for exertion even with an enlarged heart and signs of failure (twenty-seven cases) and slight cyanosis on effort or late cyanosis (thirty-one cases). Underdevelopment, though occasionally seen (eight cases), was far less frequent than in other published statistics.

The radiological features in fifty-one cases indicated their paramount importance in diagnosis. General enlargement was present in forty, chiefly to the left in thirty. The prominence of the left border proved to be due, however, to the enlarged right ventricle which displaced the left ventricle backward. Great projection of the right auricle points to coexisting mitral stenosis. The bulging of the pulmonary stem and conus with the enlarged, dense, right hilum shadow (right branch of the pulmonary artery) gives the heart its striking appearance in the anterior view. Excessive pulsation of the hilum was noticed in thirty-one instances; but a real "hilar dance" could be seen in only five, and then there was not always pulmonary incompetence. Lack of pulsation with increased density was diagnostic of local thrombosis in one necropsy case. The aorta was small or invisible in about half of the cases. In the right (I) oblique view the enlargement of the pulmonary stem and conus became even more evident, and a pulmonary impression on the esophagus was observed in eighteen of our cases. In the left (II) oblique view, the enlarged left pulmonary branch obscured the aortic window, and the right ventricle was unduly convex. Negative radiological signs of importance were the absence of the left auricular curve in the right oblique view and the absence of lung congestion. In the six cases where the left auricular curve was prominent it was proportionate to the general cardiac enlargement. Pulmonary congestion was found in only three cases having severe failure, and hydrothorax in only two—both in terminal conditions.

The electrocardiogram often helped in diagnosis. Normal rhythm was the rule (in forty-seven), and, when auricular fibrillation was present, it was not due to the lesion itself but either to rheumatism (mitral stenosis) or to age changes. Right axis deviation was very frequent (in forty-one), if we include partial right bundle branch block (26); complete right bundle branch block of the older or newer type was found in five. T_2 and T_3 were inverted independently of the bundle branch block character of the ventricular complex (in nine). A prolonged P-R interval of 0.20 second or over, and large or bifid P waves were not infrequent.

Failure appeared usually between the ages of 30 and 50 and was typically right ventricular. Late cyanosis and liver enlargement were its main features; dyspnea was moderate, and pulmonary congestion was rare except in the terminal stage when edema and ascites might supervene. Pulmonary infarction early in the course was rare and then based upon pulmonary arteriosclerosis. Subacute bacterial endocarditis as a complication was exceptional (one necropsy case). The mechanism of

failure is explained by the increased blood volume that the right ventricle has to propel, for the left atrium with its higher pressure partly diverts through the defect blood from the left cavities. We cannot accept the hypothesis recently advanced by French authors that the disproportion between right and left cavities and between pulmonary artery and aorta, respectively, is due to a congenital malformation unless A.S.D. is associated with or without mitral stenosis. The similarity of the pathologic findings in A.S.D. with or without mitral stenosis, the progressive dilatation of the right ventricle, and the often normal aorta make us reject this view.

Differential diagnosis is concerned with all congenital or acquired heart conditions in which there is a dilatation of the pulmonary artery and its branches, and these are enumerated. Pulmonary artery disease and primary dilatation of the pulmonary artery with right ventricular hypertrophy, so-called pulmonary hypertension, can produce a similar radiologic and pathologic picture. But these are exceptional conditions, while atrial septal defect is a far more likely cause of gross dilatation of the pulmonary artery and its branches.

AUTHORS.

Lowry, Frederick C., and Burn, Caspar G.: Spontaneous Rupture of the Posterior Papillary Muscle of the Heart. Arch. Path. **31**: 382, 1941.

This is a report of another case of rupture of the papillary muscle following infarction of the posterior myocardial wall. It is believed that the rupture of the necrotic papillary muscle was the result of excessive strain caused by the hypertrophied myocardium and shortened chordae tendineae of the thickened mitral valve.

AUTHORS.

Gross, Paul: Concept of Fetal Endocarditis. A General Review With Report of an Illustrative Case. Arch. Path. **31**: 163, 1941.

The occurrence of fetal endocarditis has never been established. The macroscopic and microscopic abnormalities considered criteria of fetal endocarditis have been observed also in the presence of congenital cardiac defects which, after study, have been diagnosed as noninflammatory lesions. The assumed etiological pathogen in the reported cases of fetal endocarditis has been either anamnestically absent or variable in identity.

The myocardial lesions usually seen in so-called fetal endocarditis closely resemble healed bland infarcts. Such infarctions may be related to the obliteration of arterioluminal, arteriosinusoidal and thebesian vessels by the marked parietal endocardial fibrosis.

The valvular and parietal endocardial changes seen in these cases are better explained on the basis of a developmental defect, since they show no inflammatory residua.

The case of a full-term newborn boy is reported. Stenosis of the mitral and aortic valves was present, and the condition resembled strikingly the rheumatic valvular disease of adult life. This condition was associated with hypoplasia of the root of the aorta, rudimentary development of the left ventricular cavity, the presence of a large patent ductus arteriosus, and marked diffuse parietal endocardial sclerosis of the left ventricle. The genesis of these lesions is considered noninflammatory because of the lack of inflammatory residua.

AUTHOR.

Koletsky, Simon: Congenital Bicuspid Pulmonary Valves. Arch. Path. 31: 338, 1941.

In 3,600 consecutive autopsies congenital bicuspid pulmonary valve was found in eight (0.22 per cent). Three of these valves occurred in infants and children, and five in adults; five were in males and three in females. In the same group of autopsies were found twenty congenital bicuspid aortic valves, six pulmonary valves, with four cusps, and no aortic valves with four cusps. Two of the bicuspid pulmonary valves were isolated findings, while the remaining ones were associated with other cardiac anomalies. These were the tetralogy of Fallot, bicuspid aortic valve, patent interventricular septum, transposition of the great arterial trunks, cor biatriatum triloculare, and widely patent foramen ovale.

Morphologically, there were three types of bicuspid pulmonary valve: (1) the simple bicuspid valve; (2) the bicuspid valve in which one of the cusps revealed a congenital ridge in the sinus of Valsalva; (3) the bicuspid valve in which one of the cusps revealed a small fibrous band or frenum in the sinus of Valsalva. The bicuspid pulmonary valve with a congenital ridge is apparently rare.

From the genetic point of view it appears probable that in many instances the formation of the bicuspid pulmonary valve is due to faulty growth or to malposition of the septum which partitions the common arterial trunk into pulmonary artery and aorta.

The bicuspid pulmonary valves in this series were of little if any clinical significance. They were silent, and there was no functional stenosis or insufficiency; the occurrence of such an anomaly was usually incidental to far more serious cardiac deformities. None of the valves showed superimposed inflammation or calcification.

AUTHOR.

Koletsky, Simon: Congenital Bicuspid Aortic Valves. Arch. Int. Med. 67: 129, 1941.

In a survey of 3,300 consecutive autopsies, congenital bicuspid aortic valve was found in eighteen cases (0.54 per cent) and was the most common single cardiac anomaly. It occurred in nine infants and children and in nine adults; fourteen of the patients were males and four females, and seven of the adults were more than 35 years old. Next in order of incidence were coarctation of the aorta (sixteen cases) and patent interventricular septum (fourteen cases). The most frequent associated cardioaortic anomalies were coarctation of the aorta, patent interventricular septum, and patent ductus arteriosus, but in nine of the eighteen cases the bicuspid aortic valve was the only congenital deformity in this region. In one instance there was also a biscuspid pulmonic valve.

In seven cases simple bicuspid valves were present, but in eleven instances there was congenital fusion of two cusps, the resultant ridge being at commissure A in six cases, at commissure B in three cases, and at both commissures in two cases; no fusion was found at commissure C. In nine cases the conjoined cusp was larger than the other cusp. The congenital ridge divided the conjoined cusp equally in all but two cases. Retraction of the ventricular aspect of the conjoined cusp opposite the ridge occurred in five cases.

So distinctive as to be practically pathognomonic is the gross character of the ridge, a narrow, hemicylindric, barlike elevation situated at the commissure, directed in the long axis of the aorta, and extending slightly into the sinus of Valsalva, sharply defined, with parallel borders, and devoid of fissures at the proximal portion. The microscopic picture is characteristic. The ridge consists almost entirely of elastica, whorled centrally and continuous laterally with that of the aortic media; the elastica usually overlaps the annulus fibrosus superficially and deeply or only superficially. Blood vessels are scanty, and there is no inflammation.

Koletsky, Simon: Acquired Bicuspid Aortic Valves. Arch. Int. Med. **67**: 157, 1941.

Eight cases of acquired bicuspid aortic valve were found in a survey of 3,500 consecutive autopsies. Seven patients were males, and one was a female, their ages ranged from 13 to 74 years. In all cases the bicuspid lesion resulted from complete fusion of the left and right coronary cusps, producing a raphe at commissure A (the left coronary—right coronary commissure), while commissures B and C were usually essentially normal. The lesion was uncomplicated in two cases, while in six cases there was superimposed organic disease; namely, four had calcific sclerosis, one had acute rheumatic valvulitis, and one had both calcific sclerosis and endocarditis lenta.

The commissural raphe consisted of a firm ridge of tissue, considerably depressed in the sinus of Valsalva, directed obliquely in the sinus, of greater height and usually of greater width distally than proximally and with a rounded outer surface which occasionally revealed a fissure indicating the line of fusion of the two cusps. Microscopically, the raphe was composed essentially of hyalinized connective tissue, the base of which rested proximally on aortic media and distally on the subvalvular endocarduim. Vascularity and inflammation were limited to the distal portion and were usually situated in the lower or the middle third of the ridge, between the ring and the free margin of the cusp.

The fusion of the leaflets was evidently due to inflammation, probably rheumatic in origin. The structure of the raphe corresponded to that of the usual rheumatic commissural lesion, and in seven of the eight cases rheumatic lesions were demonstrated in other parts of the heart. However, the degree of rheumatic involvement was generally slight, being limited essentially or largely to the aortic valve. Patients usually survive such relatively mild rheumatic heart disease and are then predisposed in later life to the development of superimposed calcific sclerosis of the aortic valve.

The commissural raphe of acquired bicuspid aortic valve differs in that it is constituted largely of relatively acellular collagenous tissue, has little or no elastica, and shows the presence or residua of other disease.

Superimposed disease of the aortic valve was not found in any of the cases in early life, but in the form of rheumatic involvement, endocarditis lenta, or calcific sclerosis it was present in seven of the nine adults. It is only with the greatest rarity that the superimposed disease actually affects the congenital ridge. The study also suggests that this congenital anomaly may predispose to calcific sclerosis.

AUTHOR.

Lisa, James R., Hirschhorn, Louis, and Hart, Crawford A.: Tumors of the Heart Arch. Int. Med. **67**: 91, 1941.

Four cases of metastatic tumors of the heart causing cardiac dysfunction are reported, and the literature is reviewed.

The outstanding feature of cardiac tumors has been the intractable failure without obvious cause. The appearance of cardiac failure or arrhythmia in association with a known malignant growth in some other organ should lead one to consider the possibility of metastasis to the heart. Roentgenologic and electrocardiographic studies are valuable aids.

AUTHORS.

Rytand, David A., and Holman, Emile: Arterial Hypertension and Section of the Splanchnic Nerves. Arch. Int. Med. **67**: 1, 1941.

Forty patients were observed who underwent section of the splanchnic nerves and removal of three pairs of lower thoracic ganglions, performed in order to relieve

arterial hypertension. The criteria usually given for selection of patients were ignored.

From a consideration of what is known about the pathologic physiology of arterial hypertension and the effects of denervation it would seem that not much could be expected from any such denervating operations.

In general the results were poor. In only one patient was there a brilliant result, although in five others there was some degree of success in reducing blood pressure. Six more patients felt better, but their arterial pressures were not lowered. In nine patients there was no change. Eleven died within a year and a half, with their condition unchanged (transient relief of symptoms occurring in five of these). Eight died within two weeks after the operation.

Such criteria as age, duration of hypertension, vascular complications in the brain and the heart, heart failure, and liability of arterial pressure were not prognostically significant. The main role in deciding the outcome seemed to be played by the presence or absence of malignant hypertension as evidenced by renal and retinal lesions.

AUTHORS.

Stead, Eugene A., Jr., and Ebert, Richard V.: Postural Hypotension: A Disease of the Sympathetic Nervous System. Arch. Int. Med. 67: 546, 1941.

Patients with postural hypotension do not pool more blood in the lower part of the body on standing than do normal subjects under similar conditions. The pooling of the normal amount of blood causes an abnormal fall in blood pressure. The reflex vasoconstriction, which maintains the arterial pressure in normal subjects under similar conditions, does not occur in patients with postural hypotension and distinguishes it from other types of poor postural adaptation.

Postural hypotension is a disease of the sympathetic nervous system. It cannot be definitely stated whether the involvement of the sympathetic system is peripheral or central. The observations reported in this study point to the interpretation that the lack of vasoconstriction in response to a fall in arterial pressure is produced by a lesion or lesions in the sympathetic centers or their efferent tracts in the central nervous system rather than by lesions in the more peripheral portions of the postural blood pressure reflex arc. In certain patients only the postural vasoconstrictor reflex is affected. If the lesions are more extensive, other signs of loss of sympathetic function may be present, such as disturbances in sweating, absence of vasoconstriction and vasodilatation, in the extremities when the temperature of the body is changed, and absence of an increase in heart rate when the blood pressure is lowered.

AUTHORS.

Eckstein, Richard W., Gregg, Donald E., and Pritchard, Walter H.: The Magnitude and Time of Development of the Collateral Circulation in Occluded Femoral, Carotid, and Coronary Arteries. Am. J. Physiol. 132: 351, 1941.

The time rate of collateral development has been studied in the femoral, carotid, and coronary arteries by means of the retrograde pressure and flow.

In the femoral artery immediately after occlusion the retrograde pressure and flow approximate 20 mm. Hg and 10 to 15 c.c. per minute, respectively. Immediately a small pulse appears, and these values rise rapidly for a few hours and then more slowly for days and weeks until pulse and flow may approach those existing in the other intact femoral artery.

In the carotid artery the initial retrograde pressure and flow are somewhat greater than in the femoral artery; a pulse is always present, and these approach more quickly the normal for the other carotid.

Following coronary occlusion the retrograde flow is nearly constant at values between 0.5 to 5.8 c.c. per minute, and than after some hours it, together with the peripheral diastolic pressure, increases very slowly to obtain sizable values in a week or so. As in coronary arteries occluded for many weeks, the major source of such retrograde flow may be the other coronary arteries.

Evidence is given to indicate that initial retrograde flow is due to increased differential pressure opening pre-existing collaterals. The mechanism for further collateral extension is not known.

In addition to the flow, the rise of the peripheral diastolic pressure in all the arteries and the peripheral pulse in femoral and carotid may serve as an index of collateral extension.

The peripheral pulse and retrograde flow are elevated following increased venous return and augmented blood pressure, but may be either increased or decreased by neosynephrine.

AUTHORS.

Sigler, Louis H.: Hyperactive Cardioinhibitory Carotid Sinus Reflex. A Possible Aid in the Diagnosis of Coronary Disease. Arch. Int. Med. 67: 177, 1941.

The normal carotid sinus mechanism is a protective adaptation to help maintain normal circulation. The adequate stimuli are changes in the intracarotid blood pressure. When the response to carotid sinus stimulation is unusually great, it is called a hyperactive carotid sinus reflex.

Hyperactivity may exhibit itself in extreme cardioinhibition, vasodepression, and cerebral manifestations.

This paper deals with an investigation of the hyperactive cardioinhibitory reflex in a series of 1,886 patients, including 1,151 males and 735 females. It was found that the reflex occurs with greater frequency and in higher degrees of response in males than in females. Its frequency and degrees of response also increase as age advances. Coronary disease is the most common condition in which the reflex occurs with the greatest frequency and the highest response. The more severe the coronary disease, the more apt the reflex is to occur and the greater its degree. Persons with other diseases and even some normal persons may present a hyperactive reflex, although not so often and to a much lesser degree.

It appears that the hyperactive cardioinhibitory carotid sinus reflex is due to lowered resistance at the synapses in the cardioinhibitory center and more so in the extracardiac and intracardiac ganglionic cells as well as in the myoneural junctions, allowing the transmission of afferent and efferent impulses in a large and at times an overwhelming volume. Coronary disease with its associated ischemia is a possible local cause for such lowering of resistance. An abnormal constitutional state and some defect in the nervous system may be other causes.

In view of the great frequency of a hyperactive reflex in coronary disease, it is recommended as a possible aid in the diagnosis of such disease in persons of the arteriosclerotic age who show suspicious signs or symptoms. It is also suggested that this reflex receive more study, since additional knowledge may help to explain the various cardiac arrhythmias and sudden, hitherto unexplained death.

AUTHOR.

Paterson, J. C.: Some Factors in the Causation of Intimal Haemorrhages and in the Precipitation of Coronary Thrombi. Canad. M. A. J. 44: 114, 1941.

The evidence supporting the hypothesis that the common cause of coronary thrombosis is an intimal hemorrhage is reviewed. Intimal hemorrhages are shown to result from the rupture of capillaries which are derived from the coronary lumen.

Some of the factors that are concerned in the rupture of intimal capillaries have been studied, and the results reported.

It is shown that increased intracapillary pressure, due to persistent hypertension, is a major factor in the formation of intimal hemorrhages and in the precipitation of coronary thrombi. As transient hypertension due to violent physical exertion or emotion will have a similar effect, these activities should be avoided by patients with coronary artery disease. This conclusion agrees with present-day clinical opinion.

The relation of vitamin C deficiency to the incidence of coronary thrombosis has been studied, and from the available evidence it is suggested that increased capillary fragility due to inadequate blood concentration of this vitamin may be concerned in the causation of some cases of coronary thrombosis. It is therefore recommended that patients with coronary artery disease be assured of an adequate vitamin C intake.

Finally, it is suggested that the calcification of atherosclerotic plaques may protect against intimal hemorrhages and coronary thrombosis. An ample calcium intake is therefore also recommended for patients with coronary artery disease.

The statistical data reported here, particularly those concerning blood plasma vitamin C concentrations, are admittedly insufficient for any definite conclusions to be drawn; they are being presented now only because the further study has been postponed indefinitely.

AUTHOR.

Weiss, Morris M.: Coronary Occlusion in the Negro. New International Clin. 4: 201, 1940.

This study indicates that there is no relative difference in the incidence of coronary occlusion in the negro and white races when such factors as social status and hypertension are considered. Coronary occlusion with myocardial infarction was found in 4.2 per cent of the negro and in 5.2 per cent of the white patients, 30 years and over, autopsied at the Louisville City Hospital from 1930 through 1938. This hospital is a municipal institution and admits only indigent individuals of both races. Coronary occlusion was found in 11.5 per cent of the negro and in 14.6 per cent of the white cases who had hypertension. Coronary occlusion in the absence of hypertension is rare in the negro and uncommon in the white patients autopsied at this hospital.

AUTHOR.

Gunter, J. U.: Thrombosis of the Pulmonary Artery in Identical Twins. Arch. Path. 31: 211, 1941.

Thrombosis in one of the main branches of the pulmonary artery is reported in each young identical twin. It is suggested that the thrombosis in the pulmonary arteries probably followed embolism from small thrombosed veins in the region of the infected middle ear in one twin and the region of the mastoid process in the other, even though such thrombosed veins were not demonstrated at autopsy.

AUTHOR.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

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